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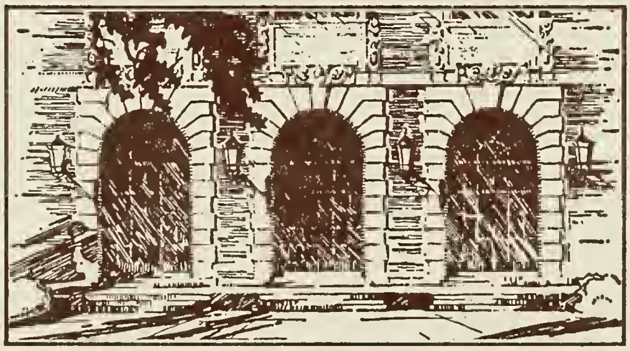

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ORGANIC SEMINAR ABSTRACTS

1970-71

Semester I

School of Chemical Sciences
Department of Chemistry
University of Illinois
Urbana, Illinois

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AFLATOXINS

Reported by Craig H. Miller September 14, 1970

INTRODUCTION

Aflatoxins are secondary metabolites of several genera of storage mold. They are extremely potent toxins and have been proven carcinogenic in a number of animals. Their isolation, characterization, and subsequent wide use in cancer research is one of the best examples of cooperation between scientists in diverse disciplines.

The production of aflatoxins by various molds, the effects of aflatoxicosis in various animals, and the problems of mold control and detoxification of toxic feeds are all treated well in a review by Goldblatt.[1] A review of the chemistry of these toxins has been attempted,[2] but the author of this seminar feels that its treatment of biochemical aspects is incomplete. It is the purpose of this seminar to acquaint the reader with the wide-spread, although poorly-publicized, problems of aflatoxin poisoning and to describe the chemistry of aflatoxins.

BACKGROUND

In 1960, British poultry farms suffered the loss of better than a million turkeys in a matter of months. The malady, appropriately termed Turkey "X" disease, was investigated for connection with the then-known bacterial toxins, and inorganic and organic poisons, but none was found.[3]

The problem was finally traced to some imported feed which was infected with a common cereal mold, Aspergillus flavus.[4] By mid 1962, two research groups had independently isolated several toxic materials from the infected feed, and investigated their fluorescence properties.[5,6] These substances were called aflatoxins (from A. flavus), and their ability to fluoresce intensely upon ultraviolet irradiation has been used throughout their investigation as a convenient means of assay.[7]

During the decade after their discovery it was found that several Aspergillus and Penicillium molds (accounting for about 60% of the microflora in farming areas[8]) produced aflatoxin,[9,10] and that nearly every food source known will sustain the growth of these molds. These molds attack damaged or overripe grains and fruit[11,12] and grow well at a variety of temperature and relative humidity levels.[13-15]

As aflatoxins are fairly heat-stable,[16] detoxification procedures usually involve washing and sorting. Chemical degradation[17] by such agents as hydrogen peroxide, ozone, ammonia, methylamine, and sodium hydroxide, and microbiological inactivation[18] have been shown possible although their commercial feasibility is not proven. Although pure aflatoxins are sensitive to ultraviolet light, irradiation of toxic meal did not prove effective in reducing aflatoxin content.[16] It was also noticed that A. flavus cultures could be induced to transform aflatoxins into less toxic or nontoxic compounds by aeration and mycelial lysis.[19]

AFLATOXICOSIS

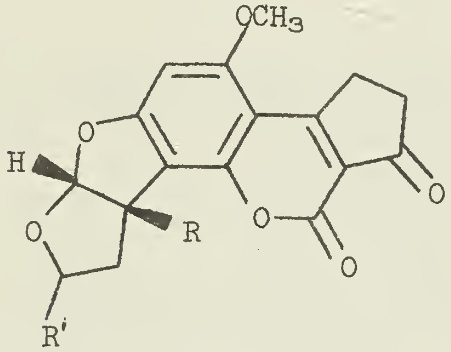
Aflatoxins have been blamed for sickness and death in a large variety of farm[20] and laboratory[21] animals. They have been shown to be carcinogenic in rats,[22] ducks,[23] and trout,[24] and there is some evidence of carcinogenic behavior in sheep,[25] mice,[26] and guinea pigs.[27] Carcinogenic reaction is usually noticed first in the liver, then in the lungs, kidneys, and lower digestive tract (although changes appear in most other organs as well).[9]

Common symptoms of aflatoxicosis are loss of appetite, lethargic behavior, and weakness of limbs, although in many animals the poisoning must be acute or these symptoms may not be noticed.[3] In cattle, aflatoxicosis results in decreased milk yield[28] and toxic milk.[29,30] In sheep, the only apparent affect is decreased fertility after long periods at high dosage levels.[25] Mortality is low in field outbreaks of the disease in chickens, and reduced growth rate is the major clinical effect.[8] Aflatoxins do not appear to be concentrated in chicken eggs.[29] Pigs are acutely responsive to aflatoxins, field outbreaks usually resulting in high mortality.[31]

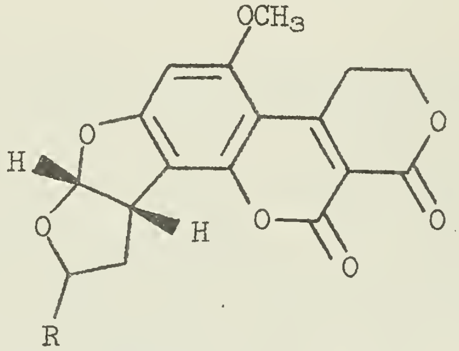
In *in vitro* studies with human tissues, it was found that 10 ppb of aflatoxin B_1 (the most potent and abundant aflatoxin) in the growth media of human embryonic lung cells caused a reduction in the mitotic rate. Levels of 0.1 to 1.0 ppm resulted in reduced DNA and protein synthesis. Throughout the range of B_1 levels, the interference with cell mitosis resulted in formation of giant cells.[32] The lethal dose of aflatoxin B_1 for human embryonic liver cells was found to be 1.0 ppm in the growth medium.[33]

ISOLATION AND STRUCTURE

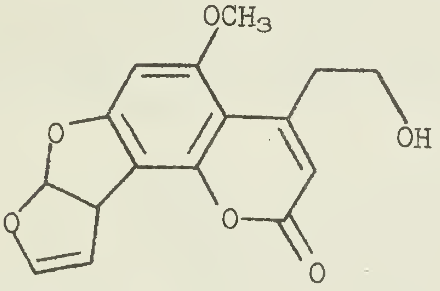
Aflatoxins are highly oxygenated polycyclic compounds with a coumarin nucleus. The ten known aflatoxins are shown in structures 1-10.



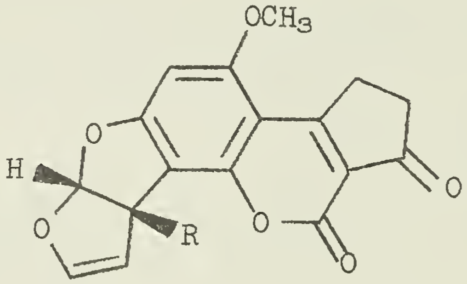
2 Aflatoxin B_2 R = H, R' = H
6 Aflatoxin M_2 R = OH, R' = H
7 Aflatoxin B_2a R = H, R' = OH



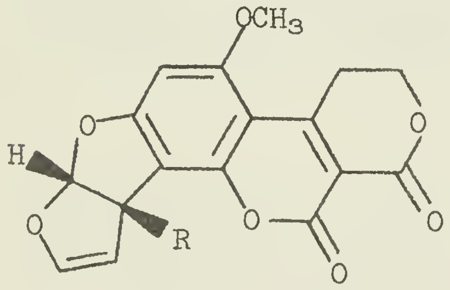
4 Aflatoxin G_2 R = H
8 Aflatoxin G_2a R = OH



9 Aflatoxin B_3



1 Aflatoxin B_1 R = H
5 Aflatoxin M_1 R = OH



3 Aflatoxin G_1 R = H
10 Aflatoxin GM_1 R = OH

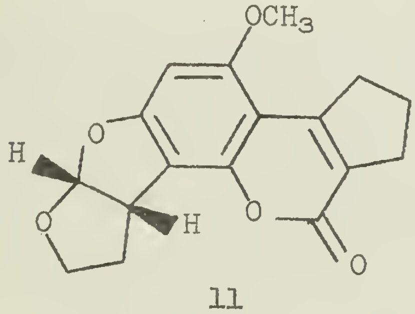
Aflatoxins B_1 and B_2 (blue fluorescence) and G_1 and G_2 (green fluorescence) were the first to be isolated.[5,6] The discovery of the structural relationship of B_1 (G_1) to B_2 (G_2) (B_2 is dihydro B_1)[34,35] was published nearly simultaneously with the structure elucidations of the B and G aflatoxins.[36,37] Aflatoxins M_1 and M_2 were first isolated from toxic cow milk,[29] but were later found in the urine of sheep fed aflatoxins and toxic nut meals. Their structures have been elucidated.[38]

Cultures of *A. flavus* have recently yielded four new aflatoxins. Two, which are hydroxy derivatives of the B and G series aflatoxins, were designated B_2a (7) and G_2a (8) respectively.[39] A third, which was named B_3 (9) because of its blue fluorescence, actually resembles a G series derivative.[40] The fourth, GM_1 (10) is the G analog of M_1.[40]

The spectral properties of aflatoxins are very instructive and were of great importance in their structure elucidations. The ultraviolet spectra of all aflatoxins show absorptions at approximately 223, 265, and 363 nm. In their work on the structure of B_1, Büchi and his co-workers[36,37] found that tetrahydrodeoxoaflatoxin B_1 (11) (formed by absorption of three equivalents of hydrogen over Pd-C by B_1) exhibited nearly the same ultraviolet trace as did the synthetic coumarin 12. Furthermore, the spectra of other dialkoxycoumarins were sufficiently different to allow the conclusion that 11 is a 5,7-dialkoxycoumarin.[37]

The infrared spectra of aflatoxins are also very similar to one another, although not tremendously helpful in structure determination.[36] The bands in the carbonyl region (~1760 cm^{-1} and 1685-1695 cm^{-1}) require the cross conjugation of the two carbonyl systems (ketone-coumarin and lactone-coumarin).[37] Absorption in the 3400-3600 cm^{-1} regions is absent for B_1, B_2, G_1, and G_2, but present, of course, for structures 5-10, the hydroxy aflatoxins.[2,40]

The nmr spectra are perhaps the most instructive. There are only twelve to fifteen protons in aflatoxins, and these are nicely placed for spectral analysis. For example, in the structure determination of B_1[36,37] only one benzenoid proton was found. Its chemical shift (δ 6.51) agreed well with that of sterigmatocystin (26) (δ 6.45), the structure of which is known.[41] Furthermore, the chemical shift of the aromatic resonance of tetrahydrodeoxo-B_1 is nearly the same (δ 6.30) as that of the coumarin 13 (δ 6.27).[37] Three protons show up as a methoxy singlet (δ 4.02), and four protons form an A_2B_2 absorption at δ 3.42 and 2.61, indicating that two adjacent saturated positions on the cyclopentenone ring are fully substituted with hydrogens. The pattern seen for the remaining four protons, δ 6.89 (1 H, d, J = 7 Hz, H_a), 6.52 (1 H, t, J = 2.5 Hz, H_c), 5.53 (1 H, t, J = 2.5 Hz, H_d), 4.81 (1 H, t of d, J = 2.5 and 7 Hz, H_b) is identical to that found in 2,3-dihydrofuran and can be explained by the three coupling constants J_{bc}, J_{bd}, and J_{cd}, being equal as in 14 and 15.[37] The structures of the other aflatoxins can be similarly deduced by nmr.[37,38]



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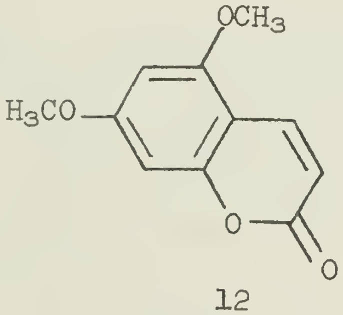

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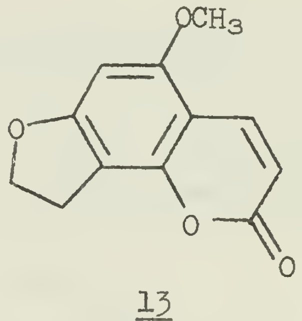

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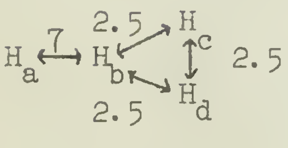

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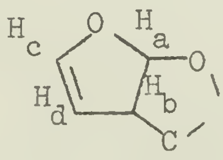

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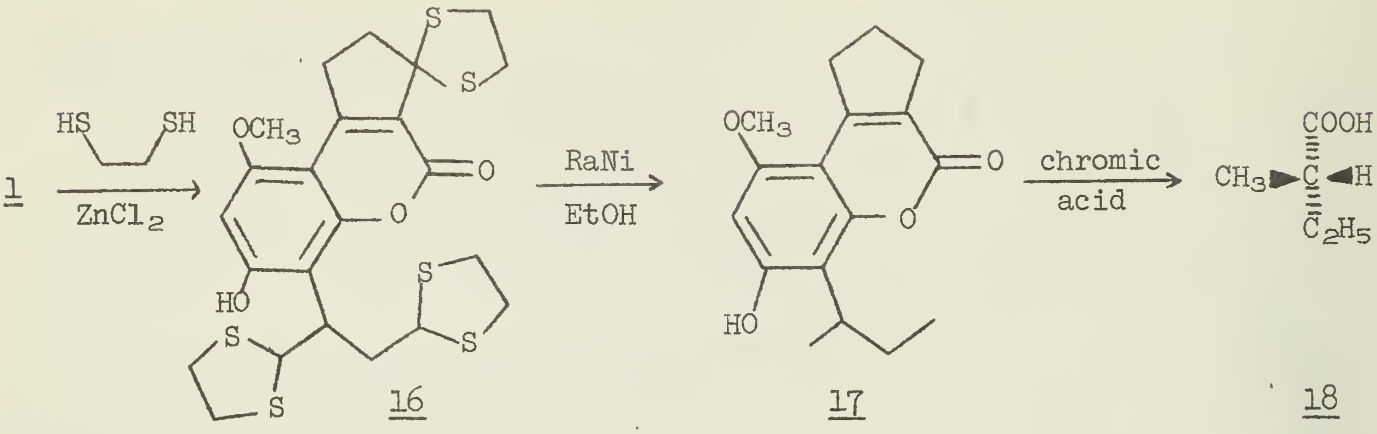
The absolute stereochemistry of the B and G series aflatoxins has been determined by Brechbühler.[42] Aflatoxin B_1 was transformed to the trithioketal 16 and desulfurized to phenol 17. Kuhn-Roth oxidation of 17 gave (+)-(S)-2-methylbutanoic acid (18) in 90% yield and 99% optical purity. It follows that aflatoxin B_1 has the configuration (1).[42] Since B_2 (G_2) and B_2a (G_2a) can be made directly from B_1 (G_1), and since G_1 and B_1 have essentially superimposable circular dichroism curves, all B and G series aflatoxins have the same configuration.[39,42]

Similar optical properties indicate that the M series aflatoxins, too, have the stereochemistry shown.[38]

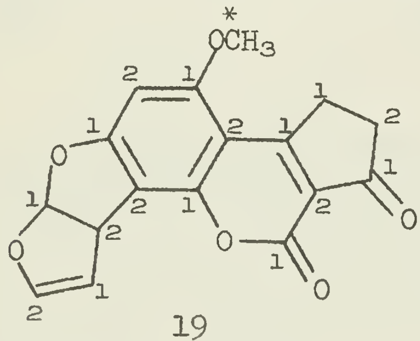


Chromatography has played an indispensable role in the isolation of aflatoxins, whose similar structures make them difficult to separate. From the earliest account until very recently, complex mixtures were mistaken for pure compounds.[5,38] Dutton and Heathcote have recently developed a procedure for isolation of all the now-known aflatoxins, which, although it includes four separate chromatographic steps, is more convenient than previous methods.[39,40,43] A new thin layer plate has also been developed which is both easy to prepare and rapid developing.[44]

BIOSYNTHESIS

The question of aflatoxin biosynthesis has been the object of much postulation but few published experimental results. It has been suggested that sterigmatocystin (26)[45] and kojic acid (5-hydroxy-2-hydroxymethyl-1,4-pyrone)[46] could be intermediates in the biosynthetic pathway, but both of these suggestions lack experimental confirmation.[2,47] More recent work has shown that a number of radioactive precursors are incorporated by A. flavus into aflatoxins,[48] but many of these are broken down to acetate before incorporation.[49]

The most impressive work has been done in Büchi's laboratory.[50-52] Methyl-^{14}C-methionine and [1-^{14}C]- and [2-^{14}C]-acetate have been incorporated into aflatoxin B_1, and the B_1 degraded to establish the exact position of the activity. The methyl-^{14}C-methionine labelled the methoxy carbon of B_1 specifically (98% recovery of radioactivity).[50] The acetate studies revealed nine positions labelled by [1-^{14}C]-acetate and seven positions labelled by [2-^{14}C]-acetate. The labelling pattern is shown in 19.[51]



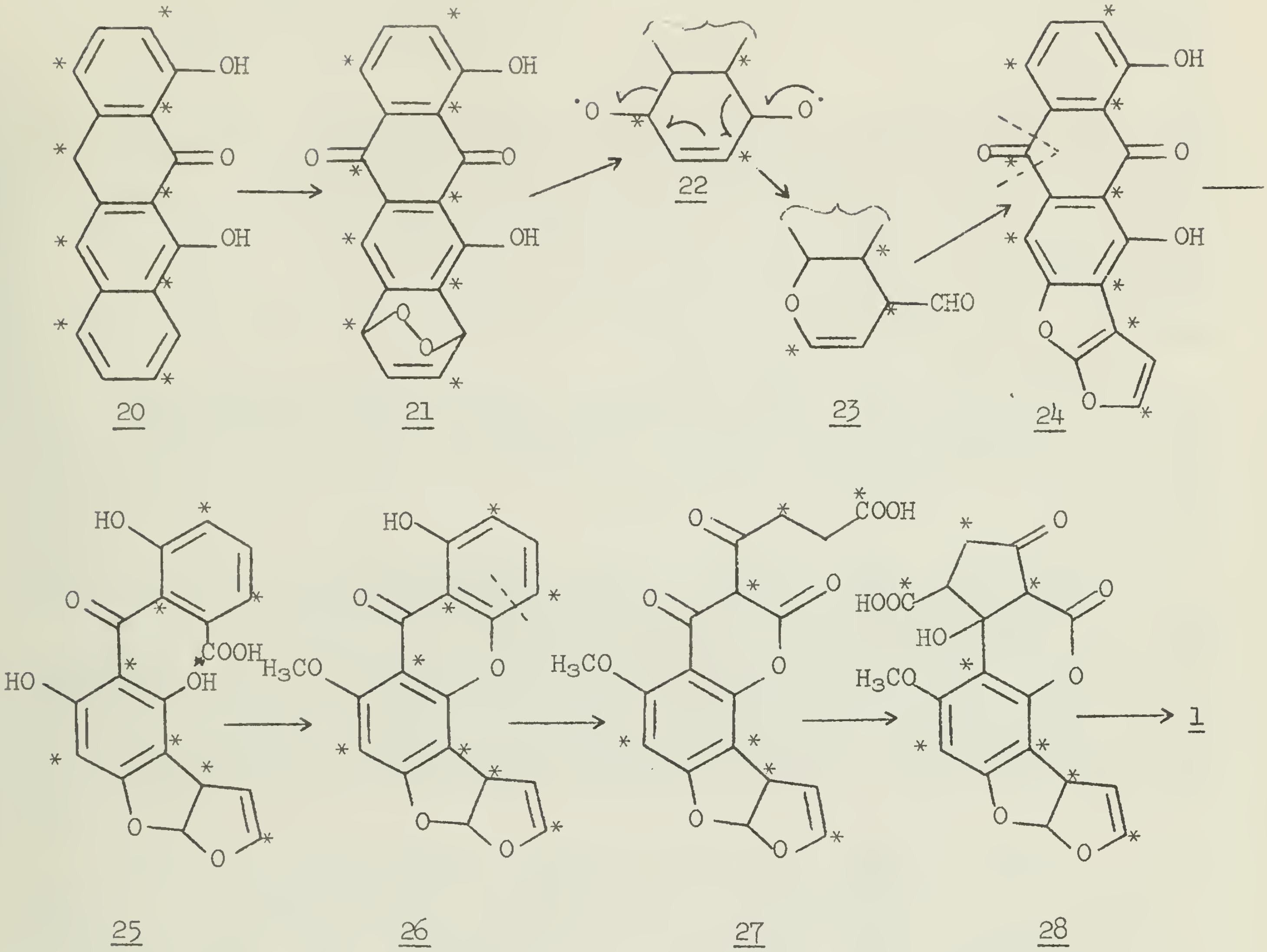
19

$*CH_3S(CH_2)_2CH(NH_2)COOH$

$\overset{2}{C}H_3\overset{1}{C}OOH$

In an attempt to explain their results, this group[51,52] postulated sterigmatocystin as an intermediate, raising the possibility that the failure of labelled sterigmatocystin to be incorporated by A. flavus in previous studies[47] could be due to permeability problems. The pathway postulated by Biollaz, Büchi, and Milne is shown in 20 through 28.

The labelling results require that two acetate methyl-derived carbon atoms be lost in the biogenesis of B_1 from a polyacetate chain. The distribution of methyl carbon atoms is shown in polyacetate-derived 20.[51]



The diradical rearrangement of 21 to 23 is without chemical precedent, but mechanistically not unreasonable.[51] The isomerization of 23 to 24 has precedence in the chemical synthesis of B_1.[53,54] Oxidative ring cleavage of 24, followed by decarboxylation, oxidation, and cyclization (not necessarily in that order) would yield sterigmatocystin 26. A second ring cleavage to the cyclopentenone with expulsion of another carbon dioxide molecule completes the scheme. The required two carbons have been lost.

In an effort to answer the question of sterigmatocystin incorporation, a cell-free extract of A. flavus has been prepared by another group. It readily incorporated ^{14}C-acetate, mevalonate, and leucine into aflatoxins, but no degradation has yet been done.[55]

MODE OF BIOLOGICAL ACTION

The first hint as to the reason for the extreme toxicity of aflatoxins was the observation that even minute quantities of B_1, B_2, G_1, or G_2 decreased the rate of incorporation of radioactive leucine into protein in liver preparations.[56] Soon, DNA synthesis was shown to decrease in the same system after aflatoxin B_1 treatment.[57] Also, inhibition of the DNA-dependent RNA-polymerase[58] and in vivo RNA synthesis[59] was reported.

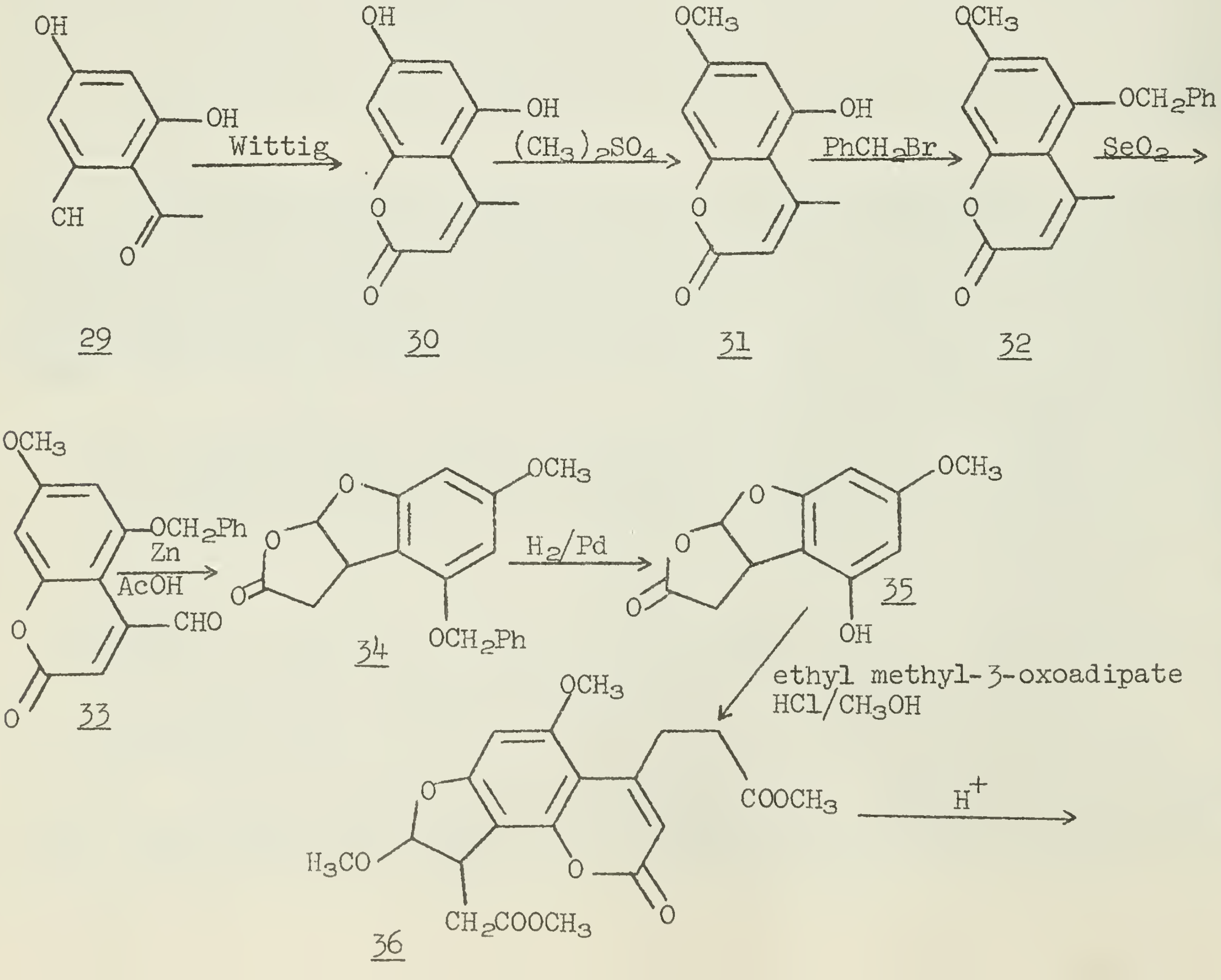
With this evidence as a guideline, binding studies were initiated. The criteria for most of the binding studies is the shift produced in the ultraviolet spectra of DNA and aflatoxin B_1. Aflatoxin B_1 was shown to bind strongly to calf-thymus DNA in vitro with an accompanying increase in viscosity of the system indicating gross conformational changes in the DNA.[60]

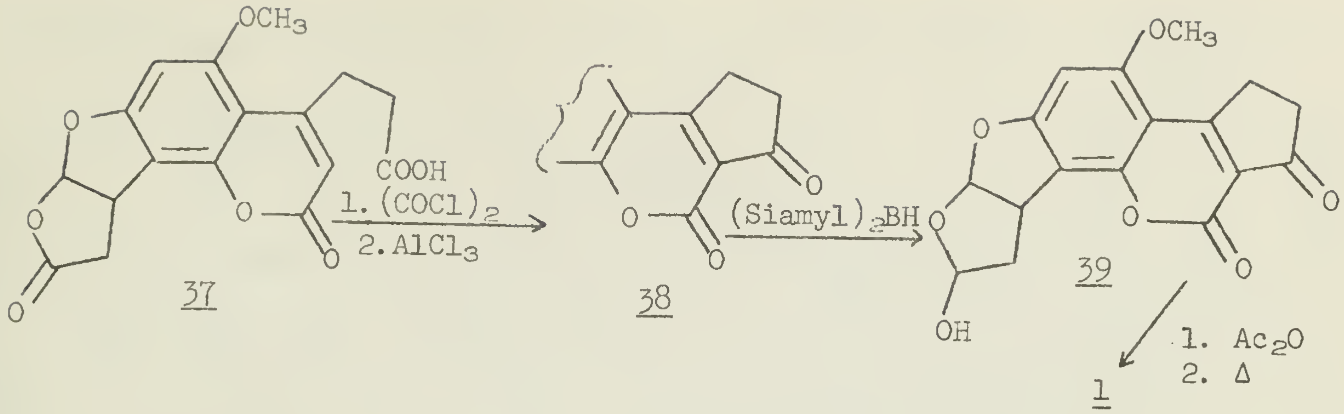
It was suggested that the purine bases (guanine and adenine) of DNA and especially the amino group of those bases had a great deal to do with the binding mechanism.[61] Evidence to this effect was gathered, although adenine was found to be much better than guanine as a binder.[62] A study involving DNA from a variety of sources showed the binding properties of B_1, G_1, and G_2 to be very dependent on the source of the DNA. The same study established nonlinearity between A-T or G-C content and binding strength. This suggests that the binding mechanism is more dependent upon base sequence than base composition.[63]

In the light of the above evidence, it has been suggested that the toxicity of the aflatoxins could stem from a strong complexation between these compounds and DNA, possibly involving hydrogen bonding with purine bases in a sequence specific manner, and this complexation impairs the replication and transcription of the DNA.[64]

SYNTHESIS

Because of the small amounts of aflatoxins (especially the G and M series) produced naturally and the difficulties involved in their separation, the preparation of pure samples of the various aflatoxins by chemical synthesis is of great importance for the continuation of biological research in this area. Büchi has described a twelve-step synthesis for racemic B_1,[53, 54] which is outlined here (see structures 29-39). A similar scheme was devised for racemic M_1.[65] Conversion of B_1 to B_2[66] and M_1 to M_2[38] has been described as straightforward hydrogenation.





Of particular interest is the conversion of 33 to 34. Treatment of 33 with zinc in acetic acid was expected to yield the saturated aldehyde which would then have to be isomerized. However, the reduction yielded the desired isomer (34).[53,54]

In the final steps of the B_1 synthesis, the cyclopentenone--lactone system is formed. Instead of ethyl methyl-3-oxoadipate,[67] 2-carbethoxycyclopentan-1,3-dione can be used, and, in fact, was used in the synthesis of M_1.[65] This reagent is the result of work by Büchi and Roberts.[68]

The problems with the synthesis of the G series aflatoxins seem to center around the formation of the coumarino--lactone function.[69] Baeyer-Villiger oxidation of B_1 has not been tried,[69] but has been discounted because one usually observes migration of the unsaturated side of the ketone or epoxidation of the unsaturation.[70]

CONCLUSIONS

Aflatoxins are a group of very wide-spread mycotoxins of extreme carcinogenicity. Although their structures and the clinical effects of aflatoxicosis are well defined, the details of their mode of action and biogenesis are still very uncertain. It will be most interesting to find out what part, if any, the aflatoxins play in the life cycle of *A. flavus.*

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ELECTROPHILIC ADDITIONS TO CYCLOPROPANES IN POLYCYCLIC SYSTEMS

Reported by Edward G. Saurborn September 17, 1970

INTRODUCTION

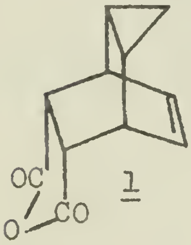
The addition of electrophilic reagents to cyclopropanes has defied generalization, in that the stereochemistry of these additions does not always occur with retention or inversion at the carbon atoms of the product to which the electrophile is bound. Equilibrating edge- and corner-protonated cyclopropanes have been invoked to account for both the contrasting stereochemical results[1,2] and mixing[1-3] of deuterium label in deuterium acid-catalyzed cleavages of cyclopropane itself. It has been generally[4-6] recognized that Markovnikov's rule applies to cyclopropane ring openings, i.e., the product usually arises from addition of the nucleophile to the site of the most stable carbonium ion. In the reactions of electrophilic reagents with cyclopropanes in polycyclic systems, the product structure will often reveal the stereochemical manner of the reagent's addition.

DISCUSSION

Treatment of (1)[13] with deuterium bromide yields[14] 2, the product[15,16] of anti-Markovnikov[7-12] addition and electrophilic retention. Addition with inversion at the site of electrophilic attack was observed in the treatment[17,18] of tricyclo[3.2.1.0^{2,4}]octane (3) with deuteriosulfuric acid in deuterioacetic acid to yield 4. Although the anti-Markovnikov addition of deuterium bromide to 1 has been attributed[14] to steric factors, and the steric environment of the cyclopropane ring in 3 is similar to that of 1, a direct comparison of these two systems is not advisable, as the basicity of the anhydride 1 is greater than that of hydrocarbon 3, and the compounds were treated with different electrophilic reagents.

Consideration of only the electrophilic retention vs. inversion gives an indication of the lack of predictability that exists in electrophilic attack of cyclopropanes. The addition of deuterium bromide to 1 is similar to additions of protic species to cyclopropanols and cyclopropyl acetates, which appear to go largely with retention of configuration.[19-21] In contrast, treatment of cyclopropanols with bromine appears to involve electrophilic attack with inversion,[19] as does treatment of 3 with deuterium acid. The electrophilic inversion with bromine has also been observed[22,23] in the addition of bromine to tetracyclo[3.2.0.0^{2,7}0^{4,6}]heptane-1,5-dicarboxylic acid. Addition of deuterioacetic acid to nortricyclene proceeds with 50% retention and 50% inversion at the site of electrophilic attack.[1,24]

Treatment of 2,8-dideuteriodibenzotricyclo[3.3.0.0^{2,8}]octadiene[25] (5) with hydrogen bromide gave 6, the product of both electrophilic and nucleophilic retention.[23] Bicyclobutane[30,31] and several alkyl substituted bicyclobutanes[26-28,31] yield[29,30] cyclopropylcarbinyl derivatives when treated with electrophilic reagents, but the addition of water to 1-cyano-3-methylbicyclobutane gives the product of cis-addition, trans-3-cyano-1-methylcyclobutanol.[32] Electrophilic reagents also add to bullvalene,[33] giving the product of 1,4-addition across the vinylcyclopropane.[34]



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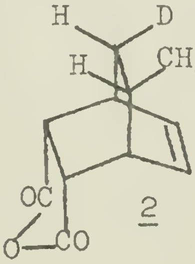

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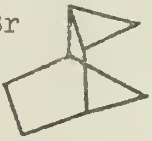

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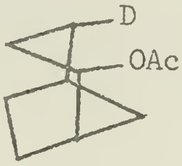

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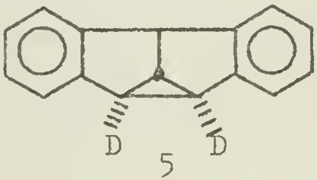

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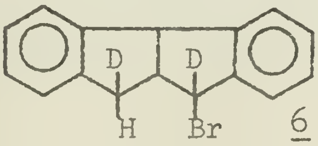

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NEW METHODOLOGY AND STERIC CONTROL DERIVED FROM PROSTAGLANDIN SYNTHESIS

Reported by Charles R. Frihart September 28, 1970

Prostaglandins constitute a group of highly biologically active naturally occurring C_{20} carboxylic acids.$^{1-5}$ Since fractionation of animal sources cannot provide large quantities of pure prostaglandins due to the difficulty of separating natural isomeric mixtures, many groups have tried to devise simple synthetic schemes for making the derivatives of prostanoic acid, which contain keto, hydroxy, acid, and double-bond functionality.

A seminar by Edward Bertram in 1967 covered the structural, biosynthetic and early synthetic prostaglandin research very well.[6] K. R. Osterhout covered the transformations used in six of the synthetic routes,[7] but he did not discuss new methodology, steric control and protecting groups used in these synthetic pathways. Groups have synthesized PGE_1,$^{8-19}$ PGE_2,$^{19-23}$ PGE_3,^{24} PGF_1,^{10,11,15,16,19} PGF_2,$^{19-23,25}$ PGB_1,$^{12,15,26-32}$ PGA_1,^{12,15} dehydro derivatives,$^{26,27,33-36}$ deoxy derivatives$^{37-39}$ and 7-oxa derivatives.$^{40-41}$

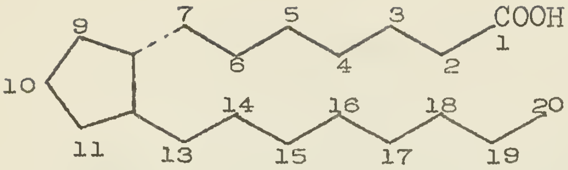
The structure of prostaglandins has caused some difficulty in their synthesis. The stability of prostaglandins is an important consideration for any synthetic scheme. While PGF is fairly stable, PGE is both acid and base sensitive as shown in Figure 2.^{4,17,42,43} PGE can be reduced to PGF_α, but PGF_α cannot be oxidized to PGE.[17]

In synthesizing prostaglandins, there are five asymmetric centers for PGF and four for PGE that one has to worry about. At present prostaglandin derivatives, such as 8-, 9-, 11- and 15-epimers and dehydro, deoxy and oxa derivatives, are important for testing as pharmacological agents[44] and as enzyme substrates.[45]

The stereochemistry of the compound was determined originally by X-ray crystallography,[46] but ORD is now most widely used to determine substitution, especially on the pentane ring.^{43,47} The two major difficulties discussed above have a large impact on the synthetic pathways discussed below.

Most synthetic routes lead to the production of PGE, which is then reduced with borohydride to give PGF_α and PGF_β. Since the beta ketol group in PGE is unstable, this group should be generated near the end of the synthesis. One way to generate the beta ketol group on the pentane ring is to solvolyze the bicyclo[3.1.0]hexane derivative (4). The two major problems with this route are the extension of the chain in going from 1 to 2 and the solvolysis of 4. The initial attempts on this route used the exo-1 as the starting material,$^{9-12}$ which was a poor choice since the endo compound reacts better in both problem steps.^{13,20,24} Exo-2 gives an $\alpha:\beta$ ratio of 35:65 (the same as by base equilibration) upon alkylation with methyl 7-iodoheptanoate, while endo-2 gives the more desired α-alkylation ($\alpha:\beta$ is 4:1), which is about the same as the base equilibration ratio of 85:15 for PGE_1. The solvolysis of the bismethanesulfonate (exo-4) using formic acid-water yields only about 5% dl-PGE_1 and 5% dl-15-epi-PGE_1 (the rest is the unrearranged monomethanesulfonate), whil solvolysis of endo-4 gives 17% dl-PGE_1 and 17% dl-15-epi-PGE_1.

Corey has used a different method in that he generates the beta ketol group in the last step. Of the possible ketol equivalents (groups which can be converted to a beta ketol) in Figure 4, Corey decided to use a nitrogen replacement since it has a range of polarity from amino to nitro groups.[17] Since it was necessary to convert the amino group to a keto group in the last step, the conditions for the conversion had to be mild enough not to convert PGE to PGA or PGB. There were two methods of converting an amino group to a ketone. In the Ruschig method the amino group is treated with NBS, followed by methoxide to create the imine and water to form the ketone.[49] The other method uses argentic salts, but the yield is low (30-60%).[50] Although it turned out that the Ruschig method was satisfactory, Corey wanted to have a method to convert the amino group under conditions milder than those used in the Ruschig method. He developed a method using



PGE$_1$ 11α,15(S)-dihydroxy-9-oxo-13-*trans*-prostenoic acid
PGE$_2$ 11α,15(S)-dihydroxy-9-oxo-5-*cis*-13-*trans*-prostadienoic acid
PGE$_3$ 11α,15(S)-dihydroxy-9-oxo-5-*cis*-13-*trans*-17-*cis*-prostatrienoic acid
PGF$_{1}\alpha$ 9α,11α,15(S)-trihydroxy-13-*trans*-prostenoic acid
PGF$_{2}\alpha$ 9α,11α,15(S)-trihydroxy-5-*cis*-13-*trans*-prostadienoic acid
PGF$_{1}\beta$ 9β,11α,15(S)-trihydroxy-13-*trans*-prostenoic acid
PGA$_1$ 15(S)-hydroxy-9-oxo-10-*cis*-13-*trans*-prostadienoic acid
PGB$_1$ 15(S)-hydroxy-9-oxo-8(12),13-*trans*-prostadienoic acid

Figure 1. Some Naturally Occurring Prostaglandins.[1-4]

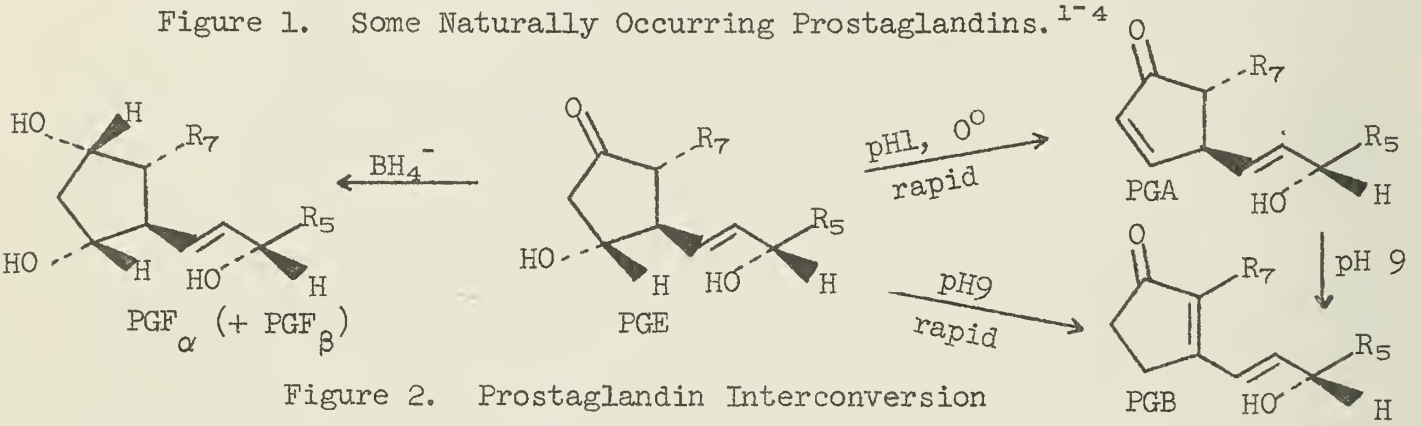


Figure 2. Prostaglandin Interconversion

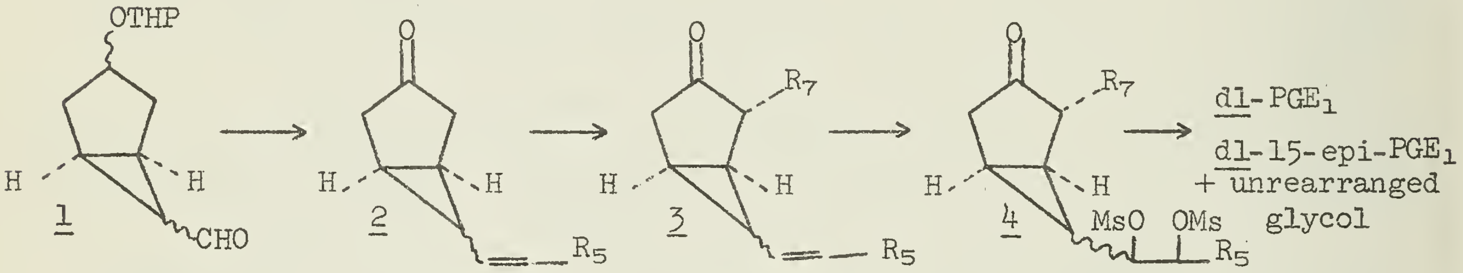
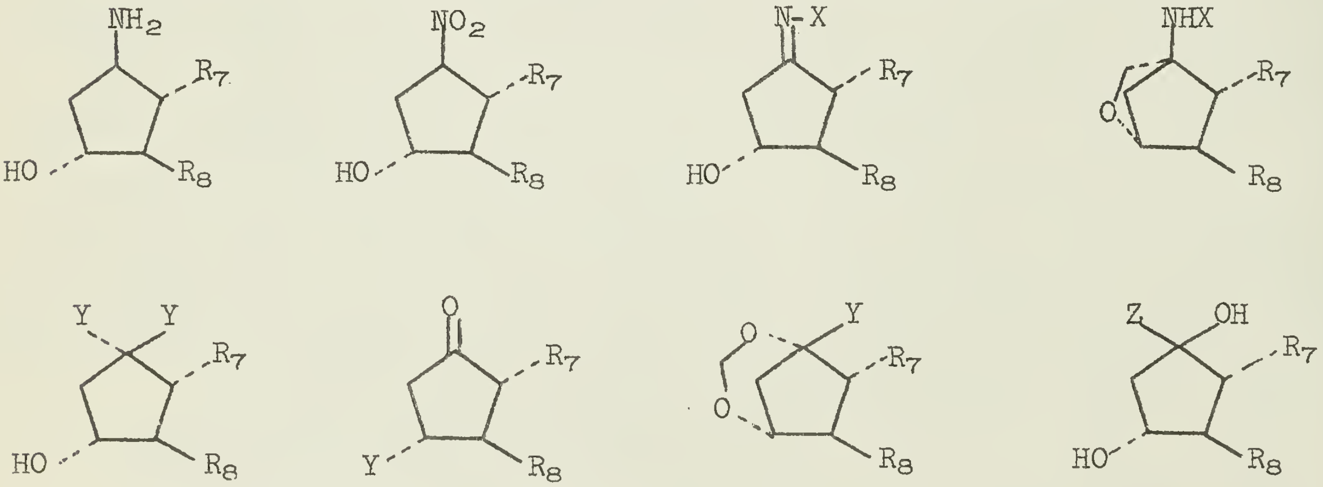


Figure 3. Synthesis Using Bicyclo[3.1.0]hexane Intermediate



Z = CH_2OH, COOH, *p*-HOC_6H_4; Y = OR, SR

Figure 4. Some Functional Equivalents of the β-ketol of PGE.[17,48]

3,5-di-t-butyl-1,2-benzoquinone (5) and di-t-butylcatechol (6) to form a Schiff base, which is a very common way for Nature to transform such functional groups.[17,51] The reaction scheme is shown in Figure 5. Both reagents react with high yields with 1° amines to form ketones, but only 6 works well with 1° amines to form aldehydes. When 5 reacts with a primary amine, the main product is a benzoxazole derivative, instead of an aldehyde.

The choice of a protecting group for the 9-position must be done with care, as is shown by the work of Finch and Fitt in which they made dl-9-methoxime-PGE_1, but were not able to hydrolyze without destroying the PGE_1 as it was formed.[14] Corey has recently devised a new mild method to remove oximes by forming the oxime-acetate and hydrolyzing with chromous acetate in water.[54] Corey's first synthesis[15] began with the condensation of 2-bromomethyl-1,3-butadiene (7) and 2-lithio-2-n-amyl-1,3-dithiane (8)[52] to form the diene (9), which was then caused to react with the dienophile (10) to give the cyclohexene derivative (11) with only small amounts of the other isomer. Aluminum-mercury amalgam reduction, formylation, dithiane-dioxalane ketal interchange, hydroxylation with osmium tetroxide and lead tetraacetate oxidation converted 11 to 12. Cyclization, using 1,5-diazabicyclo[4.3.0]-5-nonene as catalyst, followed by acylation, converted 12 to 13 and gave only small amounts of the 11-epimer. Ketone reduction using borohydride yielded 14, which was dehydrated to the enone 15 using a new method which involves reaction of the alcohol with dicyclohexylcarbodiimide by the possible route shown in Figure 7. Zinc borohydride selectively reduced enone 15 to give C_{15} epimers. The compound was deacylated, the hydroxyl groups were protected as the bis-THP derivative, the cyano group was hydrolyzed, and the formamido group was deformylated to give 16. Conversion to the ketone by the Ruschig method and silica gel chromatography gave pure dl-PGE_1 (6% overall yield from 9) and dl-15-epi-PGE_1 (6%).

The importance of the proper protecting groups in Corey's first synthesis is demonstrated by the use of a similar intermediate by Morin, Spry, Hauser, and Mueller with failure to obtain the desired product.[30] Intermediate 17 was opened to 19 using ozone, but cyclization using alkali and and pyrrolidine gave the undesired closure product 20. Similar results occurred when 18, which is very similar to the 11 used by Corey, was treated under identical oonditions. The failure of this research group to get the desired cyclization was caused by either failure to have the correct catalyst for the proper cyclization or the wrong functional groups to effect the proper cyclization.

Miyano was able to limit the aldol condensation to the desired direction, but failure to have proper protecting groups caused him trouble.[35,36] Due to the rigidity imposed by the bicyclo system (21), he obtained cyclization only in the desired direction to give 22. After pyrolysis of 22 to produce 23, he was not able to reduce the carbonyl at 15 selectively over the one at 9, which was the same problem he faced in his attempted synthesis of dl-PGE_1.[34] If he could have made the carbonyl groups non-equivalent, by protecting either one, he would have had a short and unusual synthesis of dl-PGB_1.

Corey's second synthesis was similar to the first in that the molecule was built up as a non-cyclic branched chain and then cyclization was brought between the 11 and 12 positions.[16-18] A Michael addition of 3-nitropropanal dimethylacetal (24) and 9-cyano-2-nonenal (25) in base produced the adduct 26. Treatment with the sodio derivative of dimethyl 2-oxoheptylphosphonate yielded the conjugated enone 27, which was converted to the nitro bisdioxolane 28. Cyclization using a variety of catalysts was tried. Using stannic chloride in acetone gave almost pure 11-compound with very small amounts of the 11-epimer, but addition of water produced the 11-beta epimer and 11-alpha epimer in equal amounts. After reduction of the 15-carbonyl with $ZnBH_4$ and treatment with a mild base to produce the more stable β-nitro compound, separation of 15- epimers was accomplished by silica

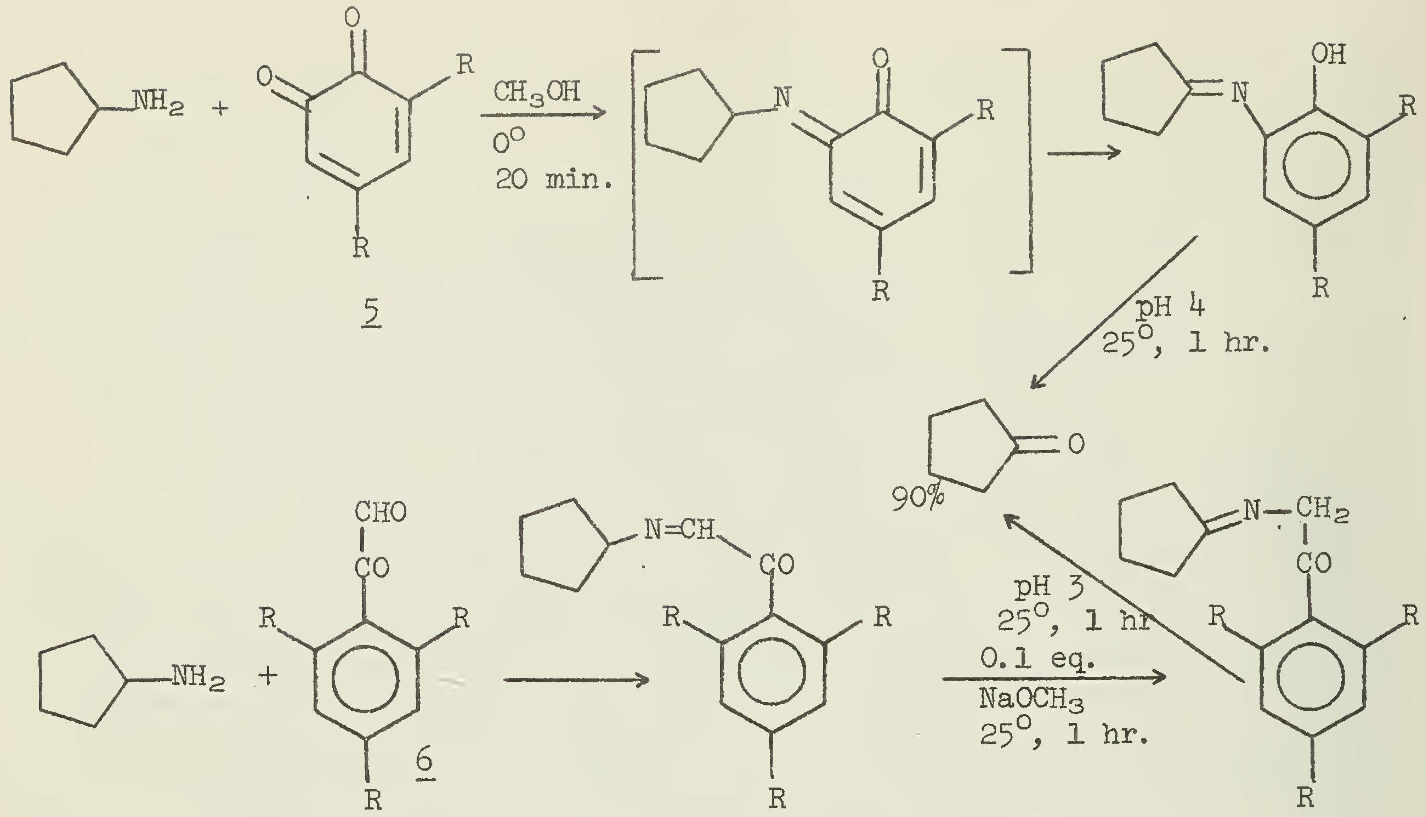


Figure 5. Conversion of Primary Amines to Ketones.

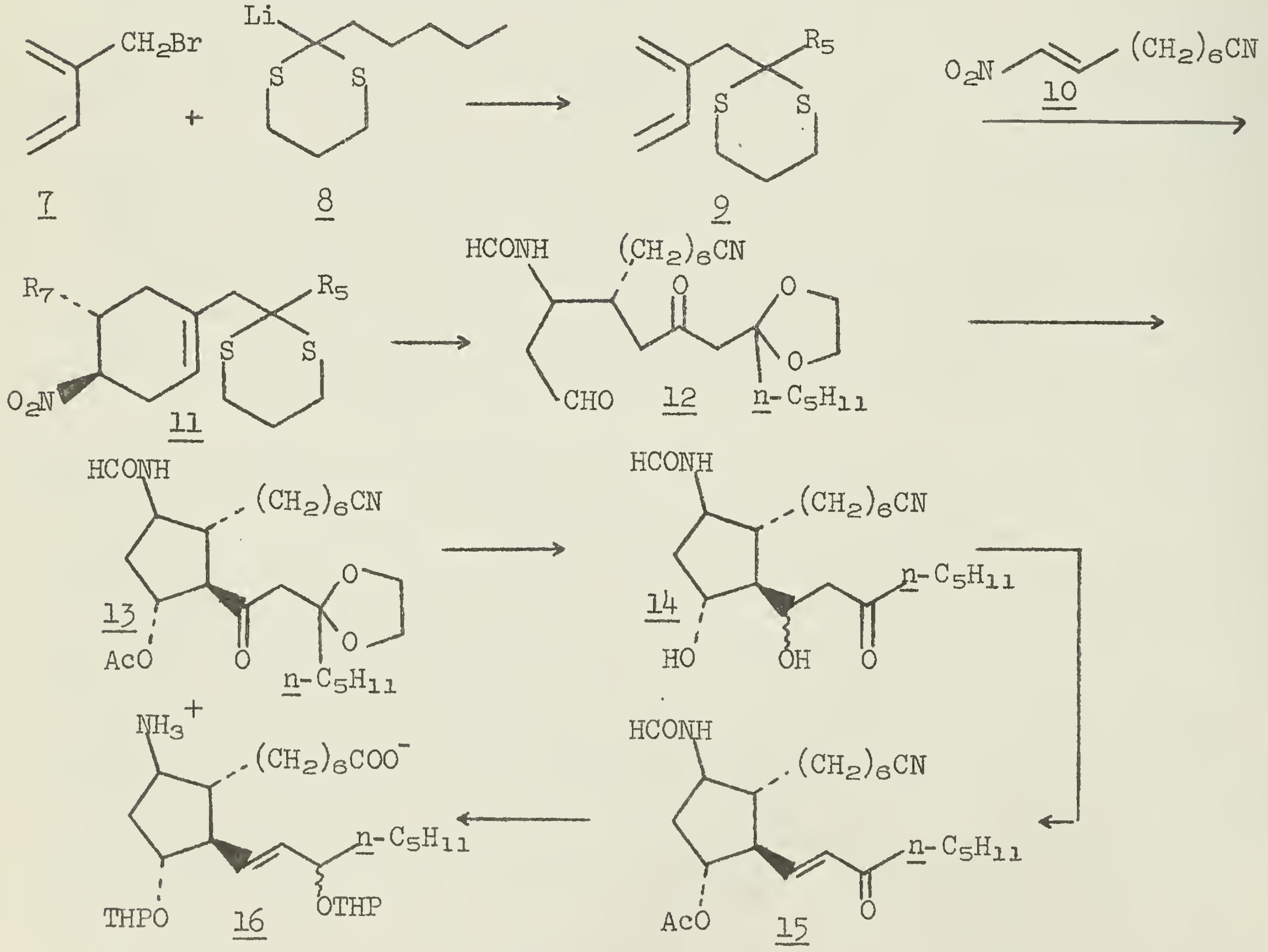


Figure 6. Some Intermediates in Corey's First Synthesis

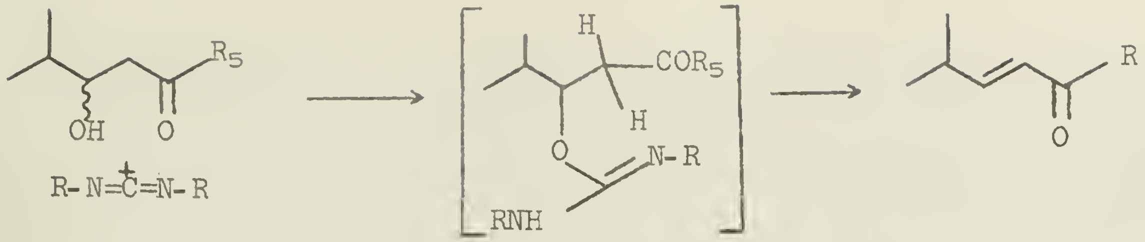
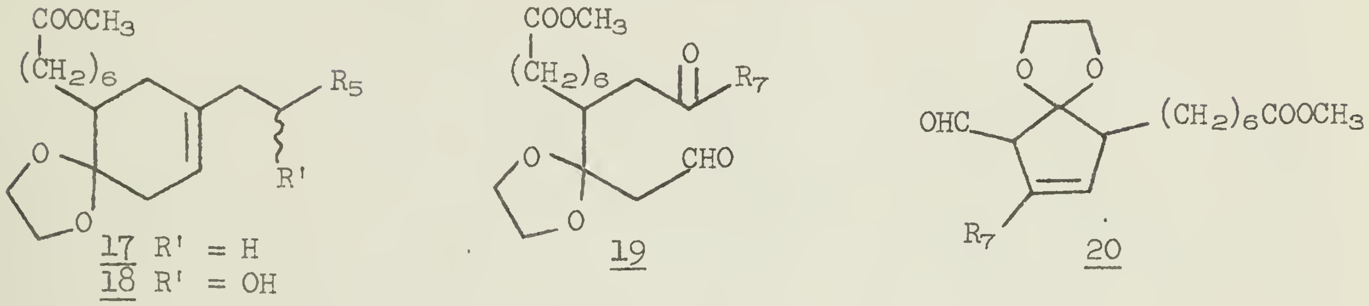


Figure 7. Dehydration with Dicyclohexylcarbodiimide

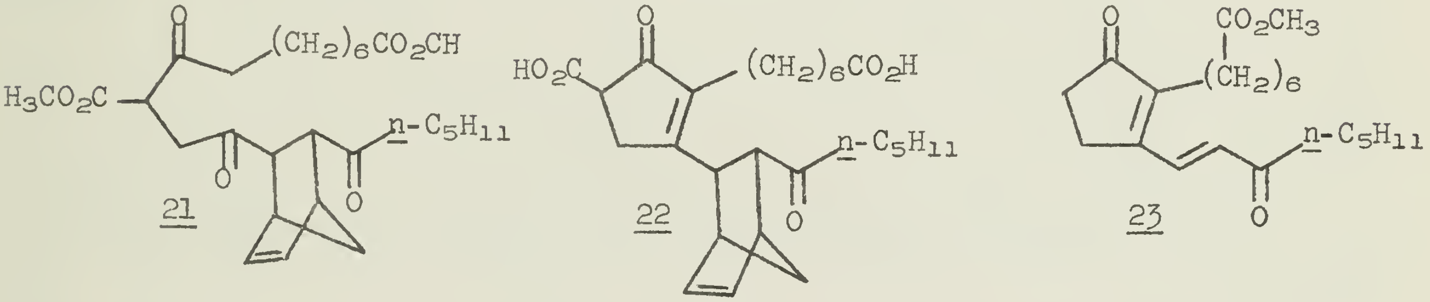


17 R' = H
18 R' = OH

19

20

Figure 8. Intermediates of Morin, *et al*.



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22

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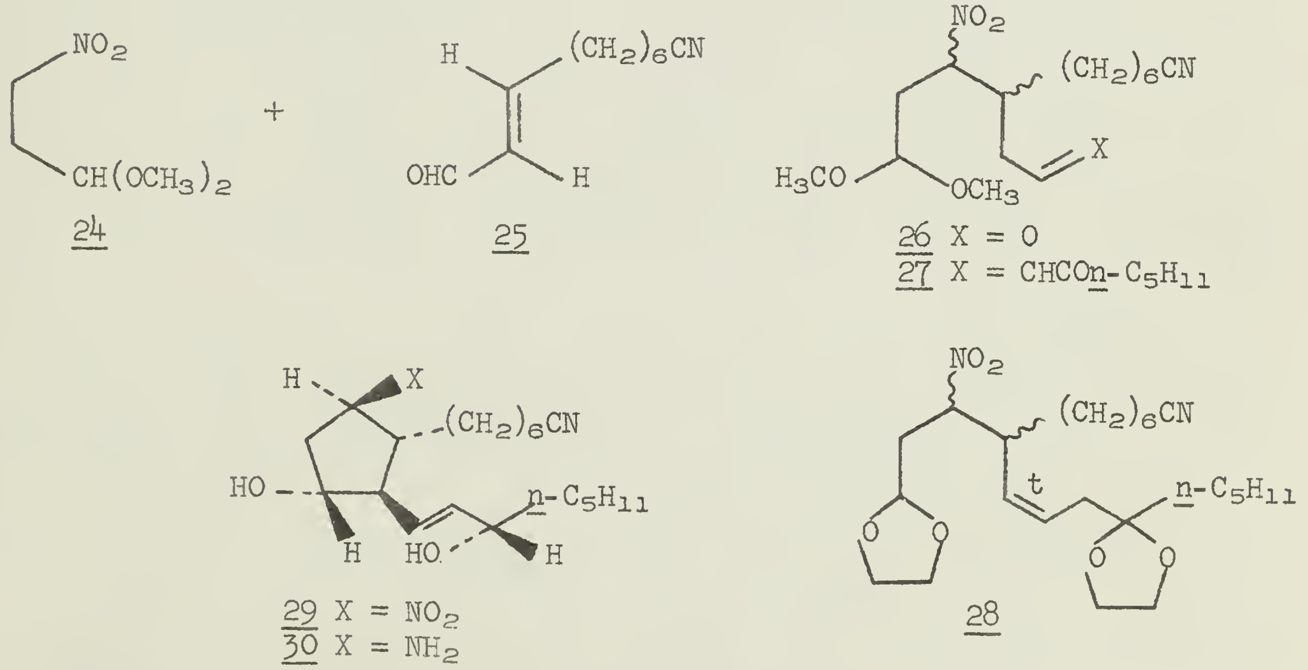
Figure 9. Intermediates of Miyano



24

25

26 X = O
27 X = CHCO*n*-C_5H_{11}

29 X = NO_2
30 X = NH_2

28

Figure 10. Intermediates of Corey's Second Synthesis

gel chromatography and the undesired 15-epi compound was reoxidized back to the 15-keto using 2,3-dicyano-5,6-dichloro-p-benzoquinone. Reduction of 29 with aluminum amalgam yielded 30, which, after resolution using (+)- and (-)-α-bromocamphor-π-sulfonic acid and conversion of the amino group to a ketone, gave both d- and l-PGE_1 (l is the natural form).

Corey's third synthesis was different from the first two in that it started with the pentane ring, to which the side chains more than added.[19, 21, 22] A Diels-Alder reaction between 5-methoxymethyl-1,3-cyclopentadiene and 2-chloroacrylnitrile produced a bicyclic compound 31 with exo-endo orientation of cyano and chloro groups, which was converted to the anti-bicyclic ketone (anti to the ether group) by reaction of potassium hydroxide in dimethyl sulfoxide. A Baeyer-Villiger oxidation formed a lactone 32 from the bicyclic ketone. At this stage the lactone was hydrolyzed to obtain the (±) hydroxy acid 33, which was resolved using (+)- and (-)-ephedrine with 60% yield. By oxidizing the alcohol to a ketone, they were able to tell which isomer they had by ORD comparison to PGA_1. Iodolactonization of 33 produced 34 (R = H). Iodolactone 34 was converted to 35 by acylation, deiodination using tributyltin hydride, and demethylation of the ether. Oxidation of 35 using Collins reagent[53] yielded the aldehyde 36, which on reaction with the sodio derivative of dimethyl 2-oxoheptylphosphonate produced the enone 37. Zinc borohydride reduced the carbonyl to give a mixture of 15α- and β-anomers, from which the desired 15α-isomer was separated and the 15β-epimer was converted back to the ketone. Removal of the acetate group, reaction with excess dihydropyran and reduction of the lactone with diisobutylaluminum hydride produced lactol 38. Condensation with the Wittig reagent derived from 5-triphenyl phosphoniopentanoic acid and sodio methylsulfinylcarbanide gave the important intermediate 39.

The stereoselective formation of the cis-$\Delta^{5,6}$ olefin was an important step in producing compound 39 in high yield. By using a reaction sequence which favored the additions to the pentane ring in the desired conformations and converting by-products to the desired isomer, Corey produced intermediate 39 from 33 in ca. 50% yield. Since 39 was resolved earlier, it produced d-PGF_2 by removal of THP groups, d-PGE_2 by oxidation using Jones reagent and removal of THP groups, l-PGF_1 by hydrogenation with palladium-on-carbon and removal of THP groups, l-PGE_1 by hydrogenation, oxidation and removal of THP groups. This third synthesis of Corey's is very useful because it can be used to produce l-PGE_1, l-PGF_1, d-PGE_2 or d-PGE_2 from 33 in at least 20% yield in each case.

Corey has devised two more synthetic routes to prostaglandins. Although these schemes gave prostaglandins in lower yields than his third route, they included good examples of stereo-control and new methods. In his fourth synthesis, Corey was able to get position-specific and stereospecific addition across an unsymmetrical double bond.[23] The anti-relationship around the central five-member ring was obvious on steric considerations when dichloroketene was added to endo-6-methoxybicyclo[3.1.0]hex-2-ene (40). Electron-supplying by the cyclopropyl or endo-methoxy group favored the intermediate 41 over addition in the opposite direction; therefore, the addition was stereospecific. The cyclopropanol 42 could not be hydrolyzed to give the hydroxy aldehyde 43 in very high yield; this problem in the ring opening of the cyclopropane ring is similar to the problem encountered by the Upjohn group (solvolysis of 4).

Corey's fifth synthesis included the use of a new reagent.[25] The steric-controlled sequence using hydroxide and iodine converts 44 to 45 in the cis-syn-cis stereochemistry as shown. Epoxidation with peracetic acid gave 89% of the desired cis-syn-cis and 11% of the cis-anti-cis product. The reaction of oxido acetal 46 with 1,3-bis(methylthio)allyllithium gave isomeric products 47, which upon hydrolysis using mercuric chloride-calcium carbonate gave a mixture of two unsaturated aldehydes 48 and 49. The reaction sequence represents the nucleophilic addition of $CH=CHCHO$.

The work on prostaglandins shows that greatest success has been achieved when the researchers have not limited themselves to existing reagents and reactions, but have invented new ones to fit their needs. By using steric-control, the yields have been increased and the purification procedures have been decreased.

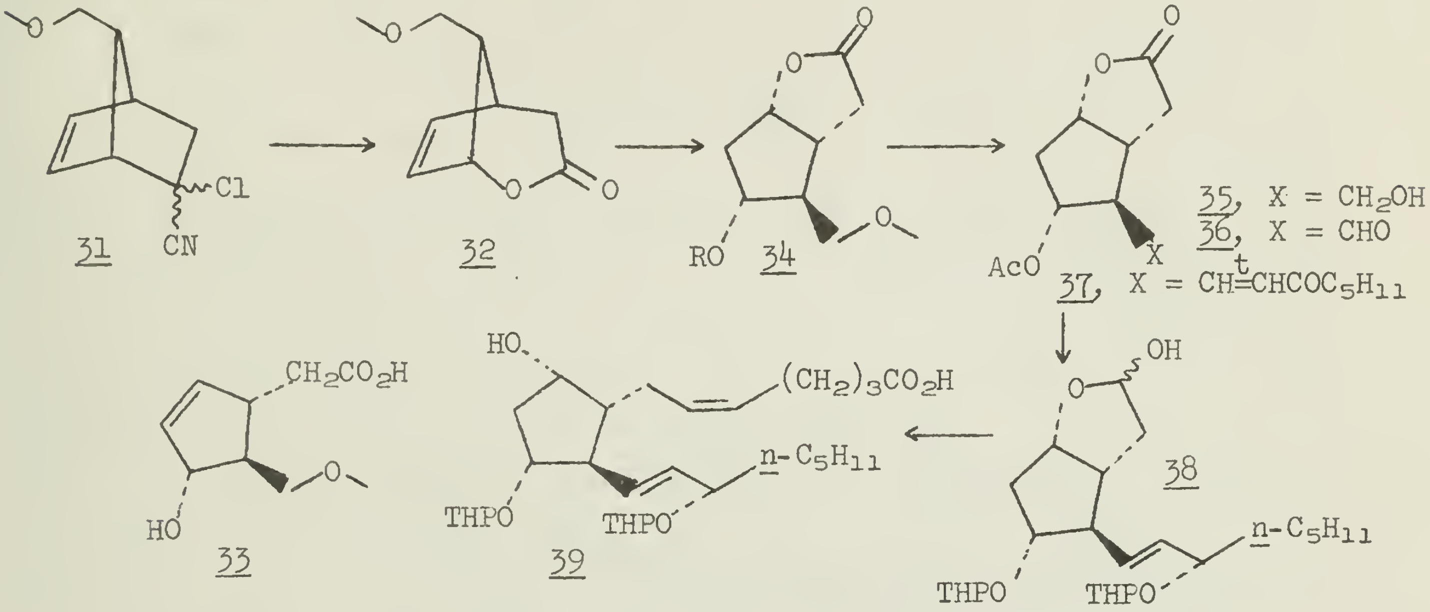


Figure 11. Intermediates of Corey's Third Synthesis

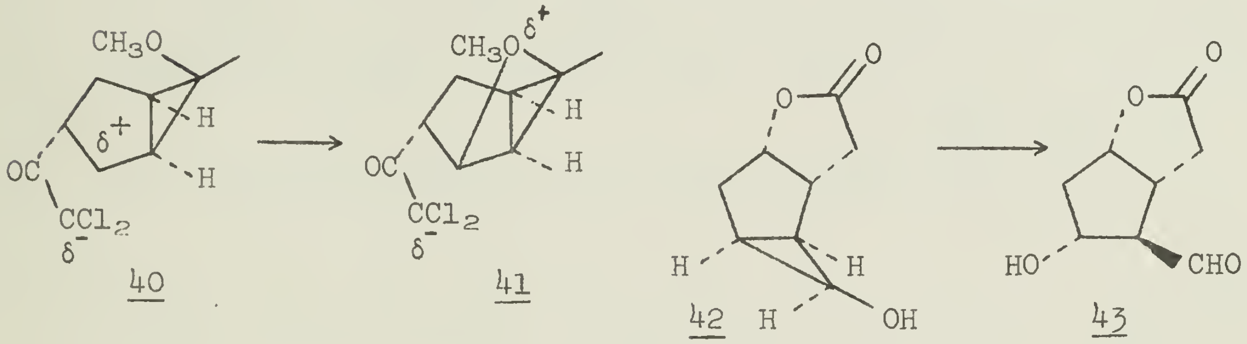


Figure 12. Corey Intermediates

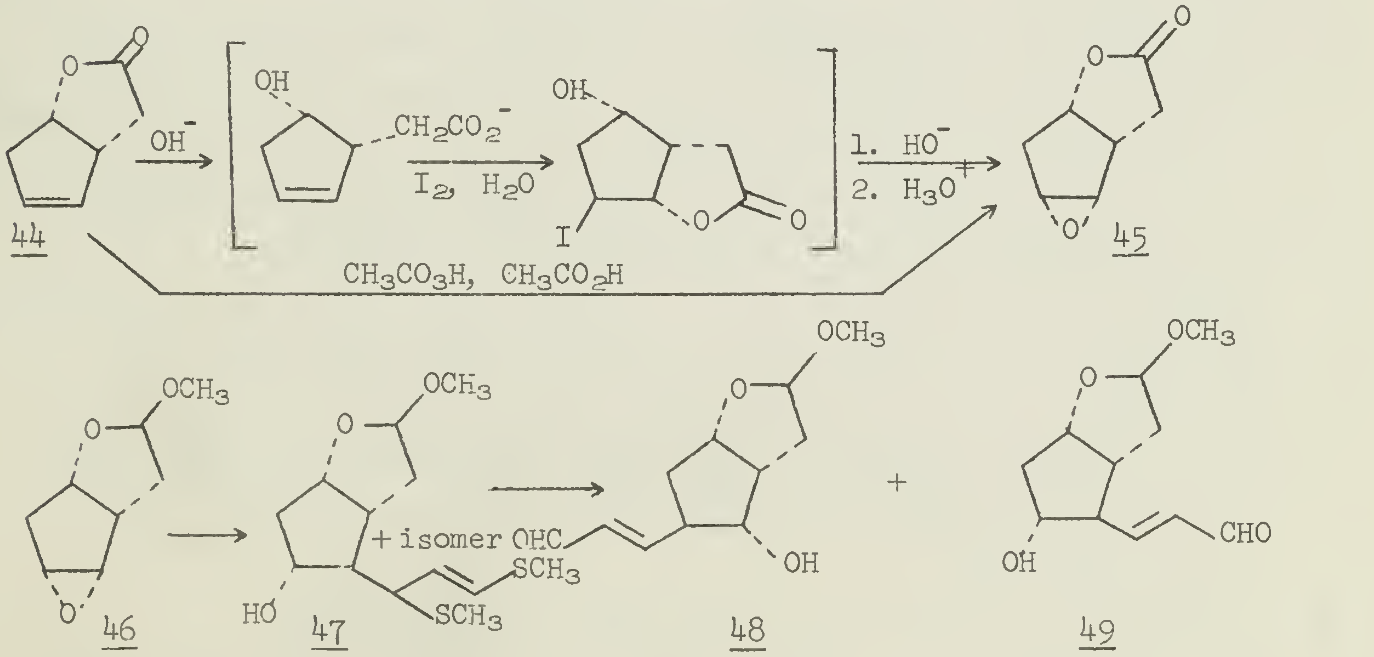


Figure 13. Corey Intermediates

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ALKYLATION AND ACYLATION REACTIONS UTILIZING THALLIUM (I) SALTS

Reported by Alan R. Branfman September 24, 1970

A frequent step in many synthetic schemes involves the reaction of an alkyl or acyl halide with a metallo-organic salt to give the desired condensation product. However, one often contends with such complications as mono- vs di-substitution, C-, O-, or N- substitution, β-diketone cleavage, Claisen condensations, and coupling resulting from air oxidation of the enol salts. Recently the utilization of thallium (I) salts has been introduced to avoid many of the above-mentioned competitive reactions.[1]

Thallium salts have been employed for the monoalkylation of β-dicarbonyl compounds to give the C-alkylated product in essentially quantitative yield.[2] The thallium (I) salt of the β-dicarbonyl compound is heated with an excess of an alkyl halide, the thallium (I) halide removed by filtration, and the product isolated by distillation. The resulting monoalkylated compounds may be converted to their respective thallium (I) salts and then alkylated with a second alkyl halide.

The simplest way to prepare the thallium (I) salts is by the addition of thallous ethoxide[3] to a solution of the β-dicarbonyl compound in an inert solvent. The thallium (I) salt crystallizes from the solution almost immediately, is collected by filtration, and can then be recrystallized. These salts are formed in quantitative yield, are crystalline, stable, non hygroscopic, and may be stored indefinitely. Thallium compounds are extremely toxic and should be handled with due care. Recently the pigment Prussian Blue has been described as a possible antidote.[4]

The thallium (I) salts of β-diketones can be acylated as well as alkylated, and the reaction can be controlled to give C- or O- acylation as illustrated in Figure I.[2] The experimental conditions for acylations are essentially the same as for the alkylations cited above. For the preparation of some typical compounds using other metal ions see references 5 to 10 at end of abstract.

Acylation, aroylation, and tosylation of phenols have also been investigated.[11] It was found that treatment of a suspension of the phenol salt in anhydrous ether with an equimolar quantity of an acyl or aroyl halide for one hour at room temperature, followed by filtration of the thallium (I) halide, produces phenol esters in high yield.

1-Acyloxy-2(1H)-pyridones have been found by Paquette to be extremely reactive "active esters," useful in the synthesis of peptides.[12] Two possible routes to this class of compounds utilizing thallium (I) salts are shown in Figures II and III.[13]

The formation of thallium (I) salts of purines and their utility in alkylations has also been reported.[14] In contrast to sodium or chloromercuri salts,[15,16] these thallium (I) salts alkylate exclusively at position 9, and this reaction has been exploited for the preparation of nucleosides as illustrated in Figure IV.

In addition to purines, phenanthridones may also be alkylated at room temperature via their thallium salts.[1] Previous procedures required formation of the potassium salt by fusion with solid potassium hydroxide, followed by alkylation in a sealed tube at elevated temperatures.[17]

We have briefly discussed the utilization of thallium (I) salts in the alkylation and acylation of a variety of straight chain and cyclic β-diketones as well as heterocyclic compounds. The use of thallium metal in organic synthesis may offer a unique tool for the preparation of compounds which are now obtained in either low yield or are unattainable by present methods.

Figure I

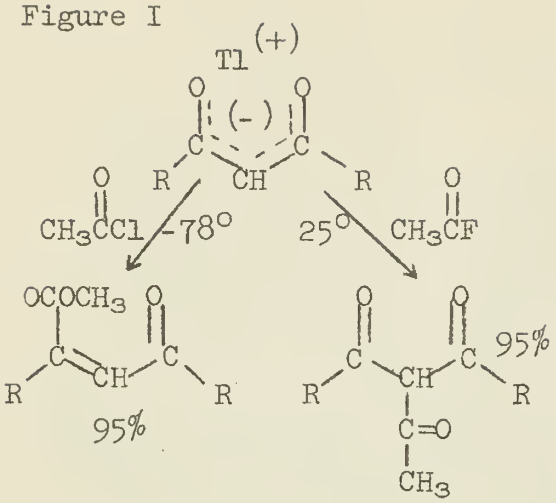


Figure II. Method A.

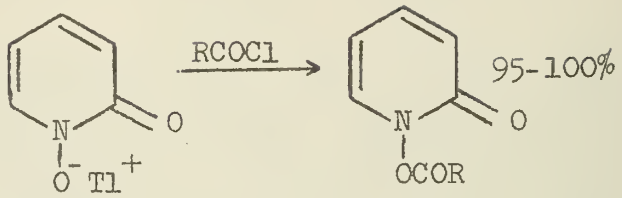


Figure III. Method B.

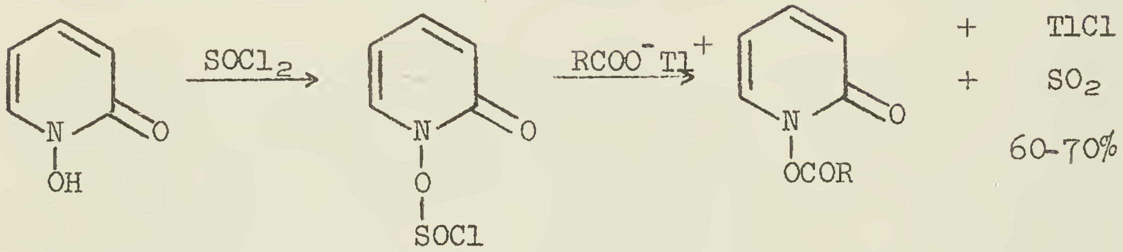
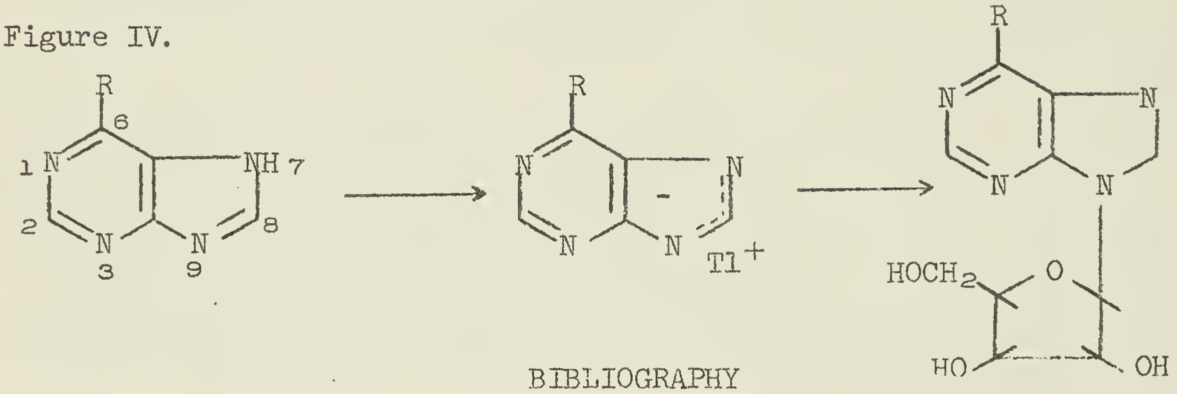


Figure IV.



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OLEFIN ADDITION REACTIONS OF DIENE PALLADIUM AND PLATINUM COMPLEXES

Reported by John Heyer October 1, 1970

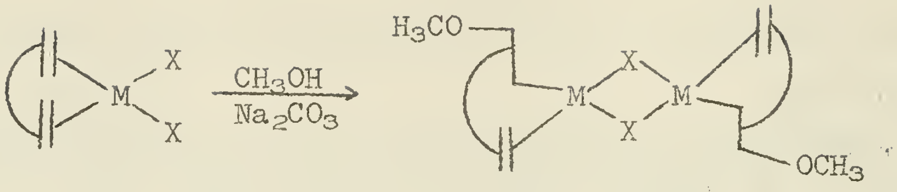
Addition reactions of several platinum (II) and palladium (II) diolefin complexes have been the subject of study by a number of authors. In these reactions a nucleophile and the metal add across one of the double bonds of a halogen-diolefinmetal complex to yield a product with the metal coordinated to the organic moiety through both a σ and a π bond. Such complexes containing σ-platinum- and palladium-carbon bonds can be isolated because of the stabilizing effect of the remaining olefin ligand of the chelate.[1]

Although what were apparently alkoxy-chlorides were reported from the reaction of dicyclopentadiene with potassium chloroplatinate in aqueous methanol or ethanol in two earlier papers,[2] the major initial research was done by Chatt and his co-workers, who reported methoxy platination[3] and palladation[4] in complexes of dicyclopentadiene, 1,5-cyclooctadiene, and dipentene through reactions of diolefinhalogenmetal complexes in methanol in the presence of a weak base such as sodium carbonate (eq 1). They assigned the halogen-bridged structure 1, with the methoxy added to the organic moiety on the basis of physical and chemical tests.[3,4] A later paper by King reporting the preparation of the chloro dimer of the methoxydicyclopentadiene-palladium complex, substantiated this conclusion.[5] Nmr studies of the complexes of dicyclopentadiene,[6-9] norbornadiene,[7,9] and 1,5-cyclooctadiene,[10] as well as deuterium labeling experiments done on dicyclopentadiene complexes,[6,7] established the addition of the nucleophile and metal across the double bond as *trans*. Single crystal X-ray structure determination of the chloro(methoxydicyclopentadiene)platinum (II) dimer confirmed the *trans* addition for this case.[11]

Other nucleophiles which have been used include nitrogen (various amines[8,12,13]), carbon (diesters,[8,14,15] β-diketones,[8,16,17] and β-keto-esters[8,15]), as well as oxygen (acetate[10,12] and other alkoxy[2-4,7]) nucleophiles. In their study of chloro(amino-4-vinylcyclohexene) and chloro(amino-1,5-hexadiene)platinum and palladium dimers, Paiaro and co-workers[13] concluded the results were better explained by a nitrogen bridged structure rather than the normal halogen-bridged one (1) on the basis of spectral and chemical evidence. With more rigid dienes such as 1,5-cyclooctadiene and norbornadiene they favored the halogen-bridged form, however, on the basis of consideration of molecular models.

When the chloro-bridged species are treated with amines such as pyridine[6-9] or *p*-toluidine,[3,4] a monomeric chloroamino(nucleophilediene)metal complex results. This is a reaction typical of chloro-bridged platinum (II) binuclear species.[3] This reaction has been used in separating the enantiomers of dicyclopentadiene by asymmetric induction by using α-phenylethylamine.[18] Similar monomers are obtained using sodium[5] and thallium[7] cyclopentadienide and triphenylphosphine.[9,12,16,17] On treating the halogen-bridged species with HCl solution, the starting dihalogendienemetal complex is normally isolated.[3,4,7] Reduction of the nucleophilic addition product with sodium borohydride[6,7,9,10,13,15] or by hydrogenation[6-8,12,14,15] yields the saturated organic species with the nucleophile attached.

The mechanism for the reaction is thought to involve attack of the nucleophile assisted by base on the coordinated olefin (eq 2).[7] The elimination of chloride, the formation of the metal-carbon bond and the attachment of nucleophile could all occur simultaneously.



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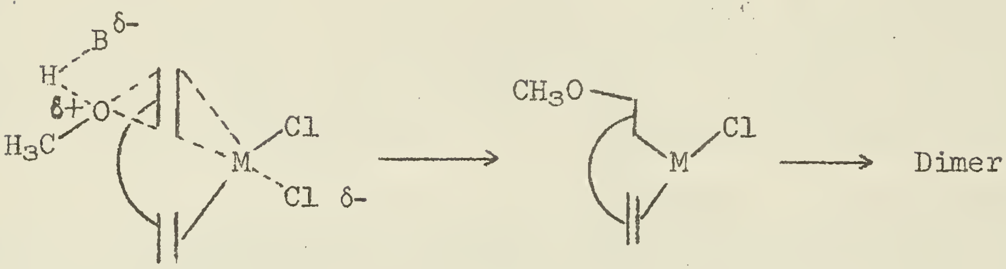

(2)

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POTENTIALLY DEGENERATE $(CH)_9^+$ SYSTEMS

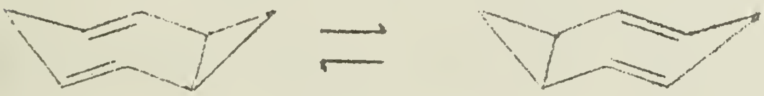
Reported by William H. Robinson, Jr. October 5, 1970

Interconvertible, potentially degenerate $(CH)_9^+$ cations represent one of the most interesting and manageable of the families of carbonium ions. Extensive studies have been carried out on partially or fully degenerate systems since the discovery of a fast and reversible valence isomerization in bicyclo[5.1.0]octa-2,5-diene (1).[1,2] The most sensational and familiar of these rearrangement processes is that of the fluxional molecule bullvalene (2), which is adequately reviewed elsewhere.[3,4] Interest in $(CH)_n^+$ cations is at least twofold: first, to investigate the products formed and, second, to identify the intermediate carbonium ions and thereby postulate the mechanistic pathway of the reaction.

In contrast to the well studied $(CH)_{2n}^+$ hydrocarbons,[5,6] only a few examples of $(CH)_{2n+1}^+$ systems are to be found in the literature, despite evidence that many of these compounds undergo valence isomerization and should be even more rearrangement-prone.[7] With the $(CH)_9^+$ cations studied to date, a wide spectrum of results has been obtained. In the case of the homocubyl cation 3, complete deuterium scrambling via a series of Wagner-Meerwein rearrangements was observed.[8,9] The 9-pentacyclo[$4.3.0.0^{2,4}.0^{3,8}.0^{5,7}$]nonyl cation 4, although potentially fully degenerate, rearranges to give only threefold trishomocyclopropenyl-type degeneracy.[10,11] No scrambling of the isotopic label was observed in solvolysis studies of the 5-tetracyclo[$4.3.0.0^{2,4}.0^{3,7}$]non-8-enyl carbonium ion 5.[7]

Another potentially degenerate system, the "antibicycloaromatic"[12,13] bicyclo[3.2.2]nonatrienyl cation 6, does not retain its structural identity, but rather rearranges to give products arising from the barbaryl cation 7.[14-19] Originally this was thought to be due to the instability of 6 owing to its predicted antibicycloaromatic character, but Winstein and his coworkers have discredited this theory and presented evidence supporting a low energy pathway by which the p-nitrobenzoate corresponding to 6 may be converted to the p-nitrobenzoate corresponding to 7 (eq. 1). They further propose that 7 undergoes a low energy threefold degenerate rearrangement (eq. 2) as well as a much slower totally degenerate process (eq. 3).

In view of the pathways described, it is interesting to speculate on what results solvolysis studies might uncover in some of the other 90 mathematically possible $(CH)_9^+$ valence isomers.



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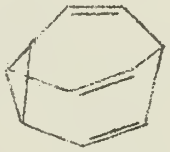

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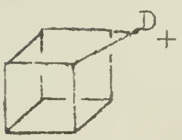

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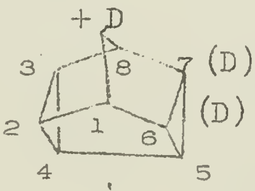

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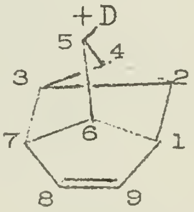

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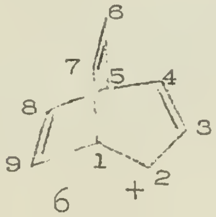

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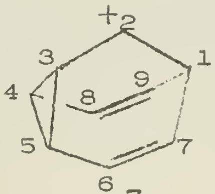

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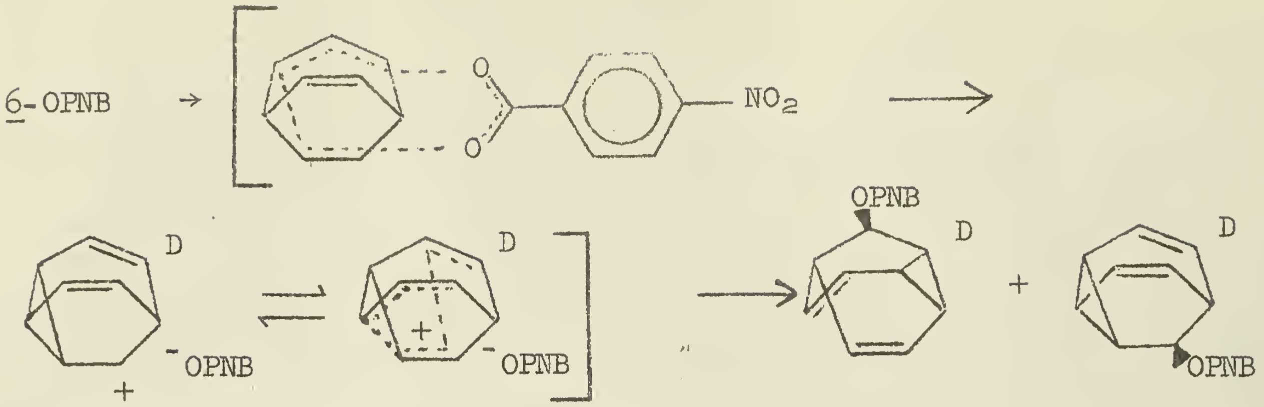

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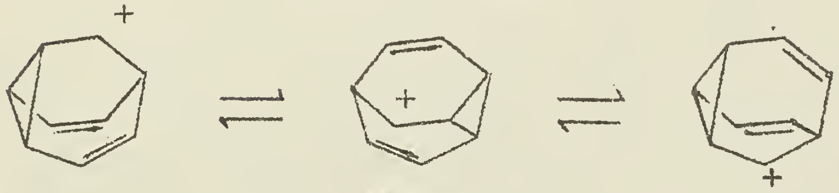

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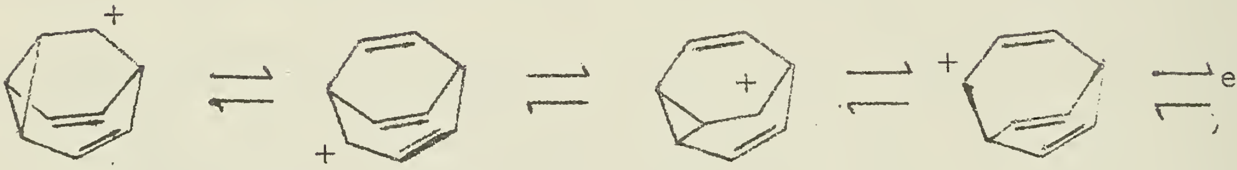

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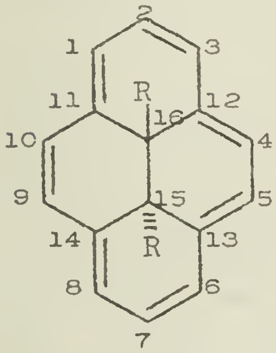
AROMATIC MOLECULES BEARING SUBSTITUENTS WITHIN THE CAVITY OF THE PI ELECTRON CLOUD

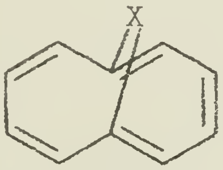
Reported by Janet Ollinger October 8, 1970

INTRODUCTION

The concept of aromaticity has been employed by organic chemists since the time of Kekulé, and the Hückel rule has aided in understanding this concept. To be aromatically stable, a molecule must be planar, conjugated, and have 4n + 2 pi electrons. The Hückel theory predicts that the pi electrons of the aromatic ring will be in a doughnut-shaped cloud above and below the plane, and presumably the center or cavity of this pi-electron cloud should be empty space. Investigations into the aromaticity of monocyclic polyenes larger than benzene bearing substituents located in the cavity of the pi-electron cloud have been made by Vogel, studying the cis-1,6-bridged cyclodecapentaenes (2a-c)[1,2] and Boekelheide, studying trans-15,16-dihydropyrenes (1a-d). This seminar will deal with the synthesis and properties of the latter compounds.



1a, R = H
b, R = CH_3
c, R = C_2H_5
d, R = C_3H_7



2a, X = CH_2
b, X = O
c, X = NR

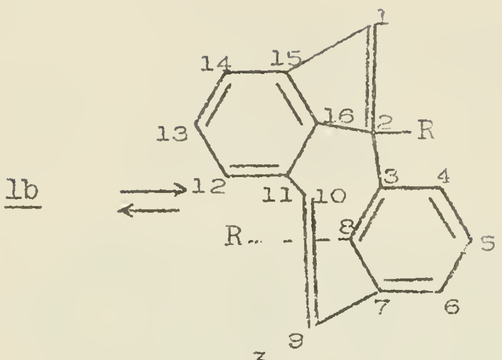
SYNTHESIS

Various synthetic approaches to the trans-15,16-dihydropyrenes have been investigated, all involving a metacyclophane intermediate.[3-16] The synthesis of 8,16-dimethyl(2.2)metacyclophane-1,9-diene (3), a valence tautomer of 1b, has been the goal of several routes,[4-11] since the possibility of an equilibrium between the two tautomers would result in dihydropyrene formation. The bridging double bonds have been introduced separately by the dehydrogenation-aromatization of cis-substituted stilbenes (4),[4-7] or simultaneously.[9-11] Initial studies involved the synthesis of 8,16-dimethyl(2.2)metacyclophane[3,6] which has been shown by X-ray[17a] and chemical[17b] studies to exist in the trans, step-like geometry shown in 5, with the methyls at the 8 and 16 positions projecting over the neighboring benzene ring. However, attempts to introduce unsaturation in the side chain of 5, as had been reported by Cram and Dewhirst[18] with paracyclophane, were unsuccessful.

Boekelheide has developed a new method for the synthesis of cyclophanes, yielding a side chain functionality which can be converted to olefinic unsaturation.[9] Formation of the metaparacyclophane 7 proceeded in 36% yield by addition of the dianion of the bis-1,3-propanethioacetal 6 to p-xylylene dibromide. Hydrolysis to the diketone proceeded in 91% yield. The frequency of the carbonyl stretch was normal, appearing at 5.90 μ, and the signal in the nmr for the internal proton at the 8 position was at τ 4.36. Conversion to the diolefin proceeded as shown.

Treatment of the dianion of 6 with m-xylylene dibromide resulted in formation of the metacyclophane analog of 7, which was successfully hydrolyzed to the diketone.[9] However, conversion to the diolefin has not been reported. Attempts to prepare the orthoparacyclophane analog of 7 were unsuccessful.[19,20]

The olefin bridge was also formed by transformation of a sulfide linkage to a carbon-carbon double bond by a Stevens rearrangement. This reaction was successful for metapara-,[21] meta-,[11,22] and 8,16-dimethylmetacyclophanes,[10,22] the latter rearranging spontaneously to trans-15,16-dimethyldihydropyrene. The synthesis of the latter is illustrated below.



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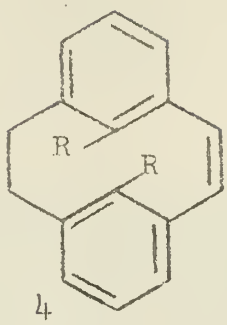

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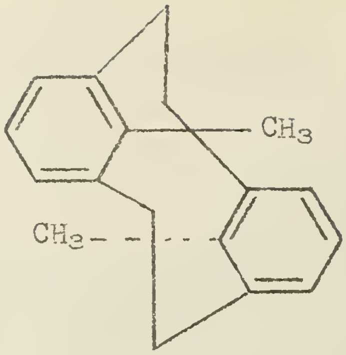

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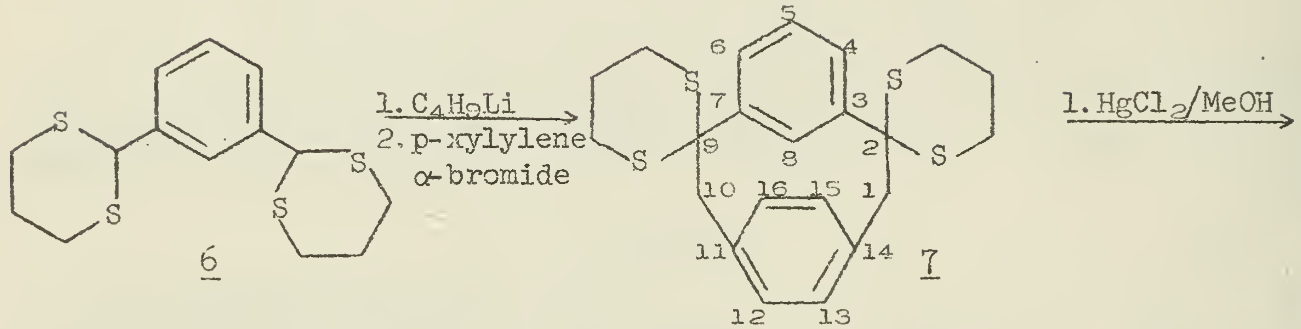

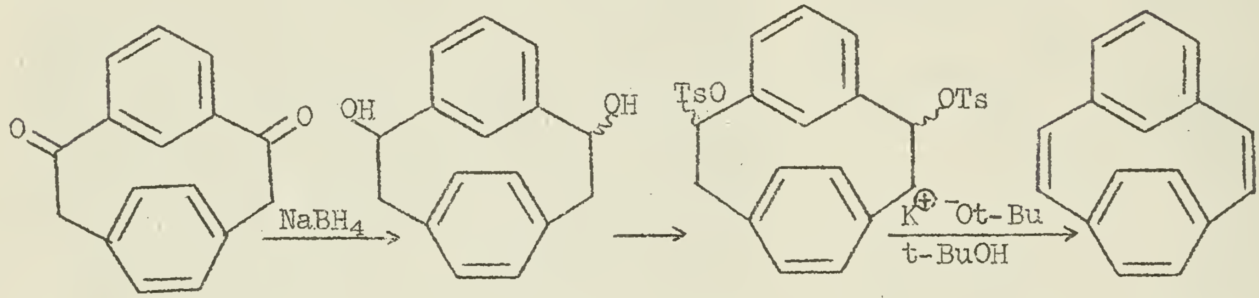

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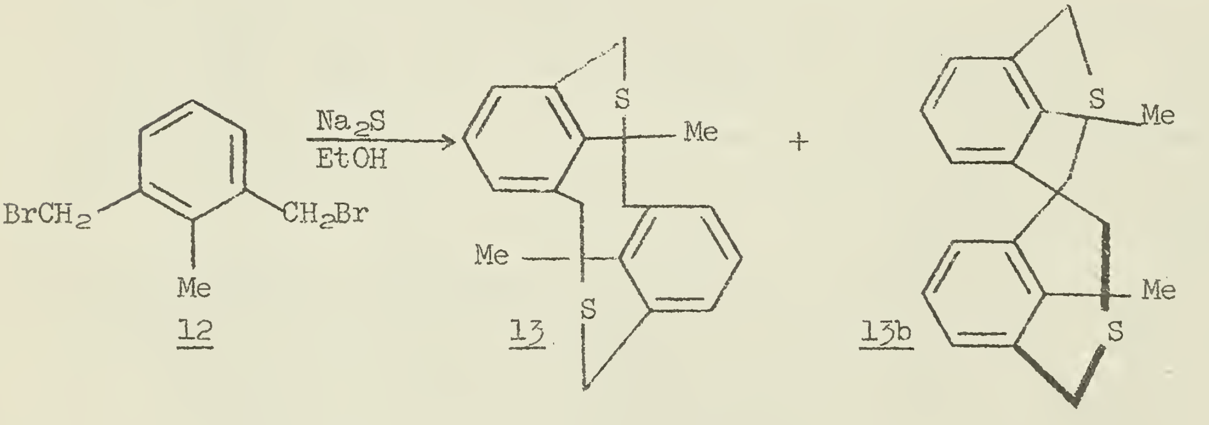
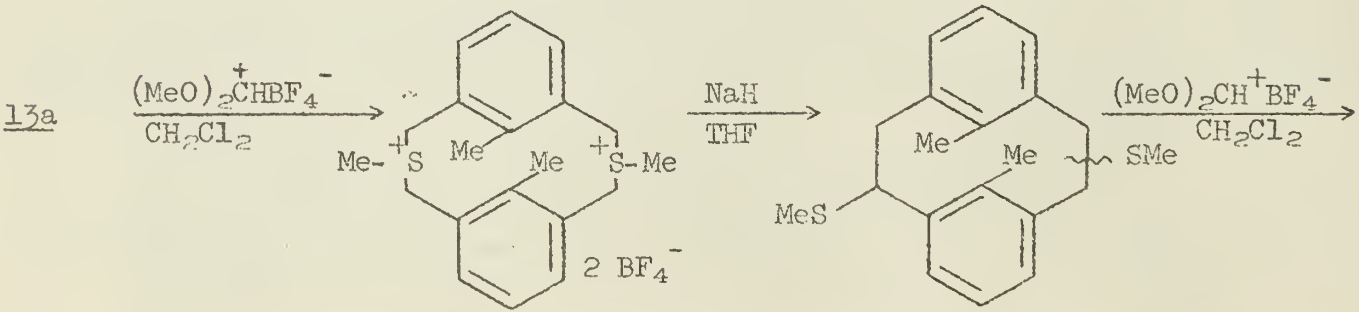
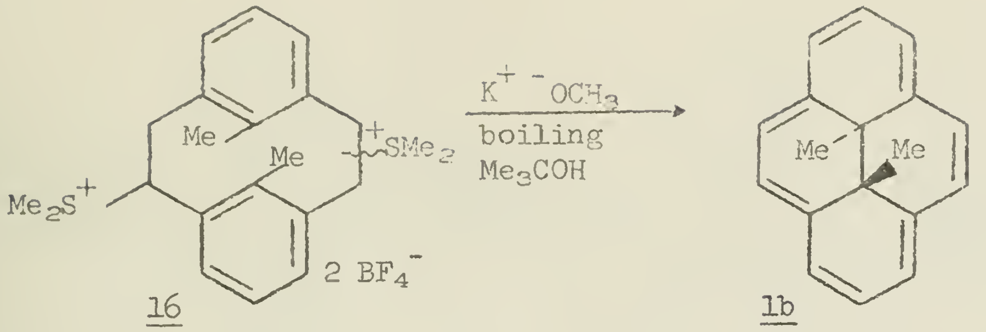




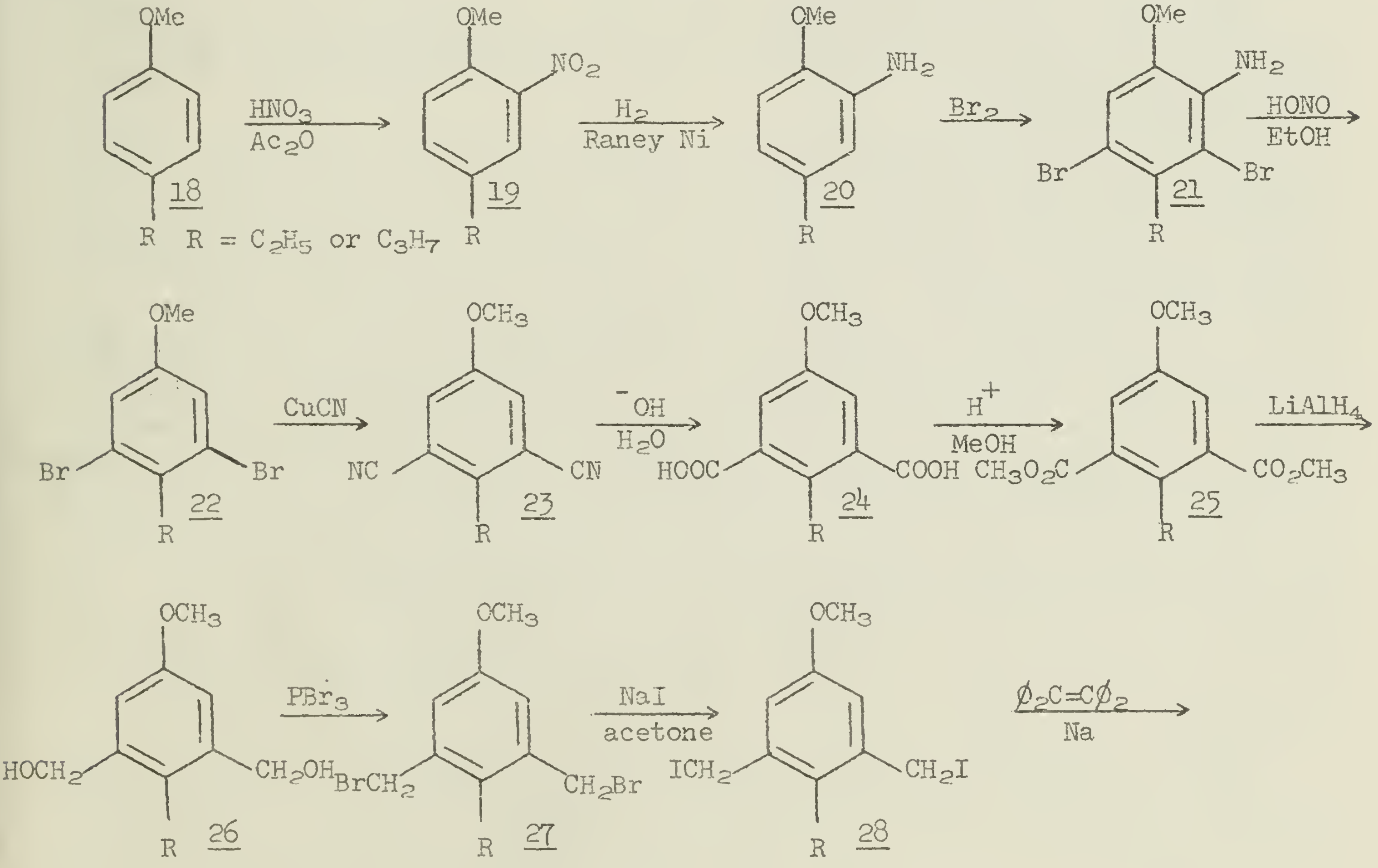
14 15

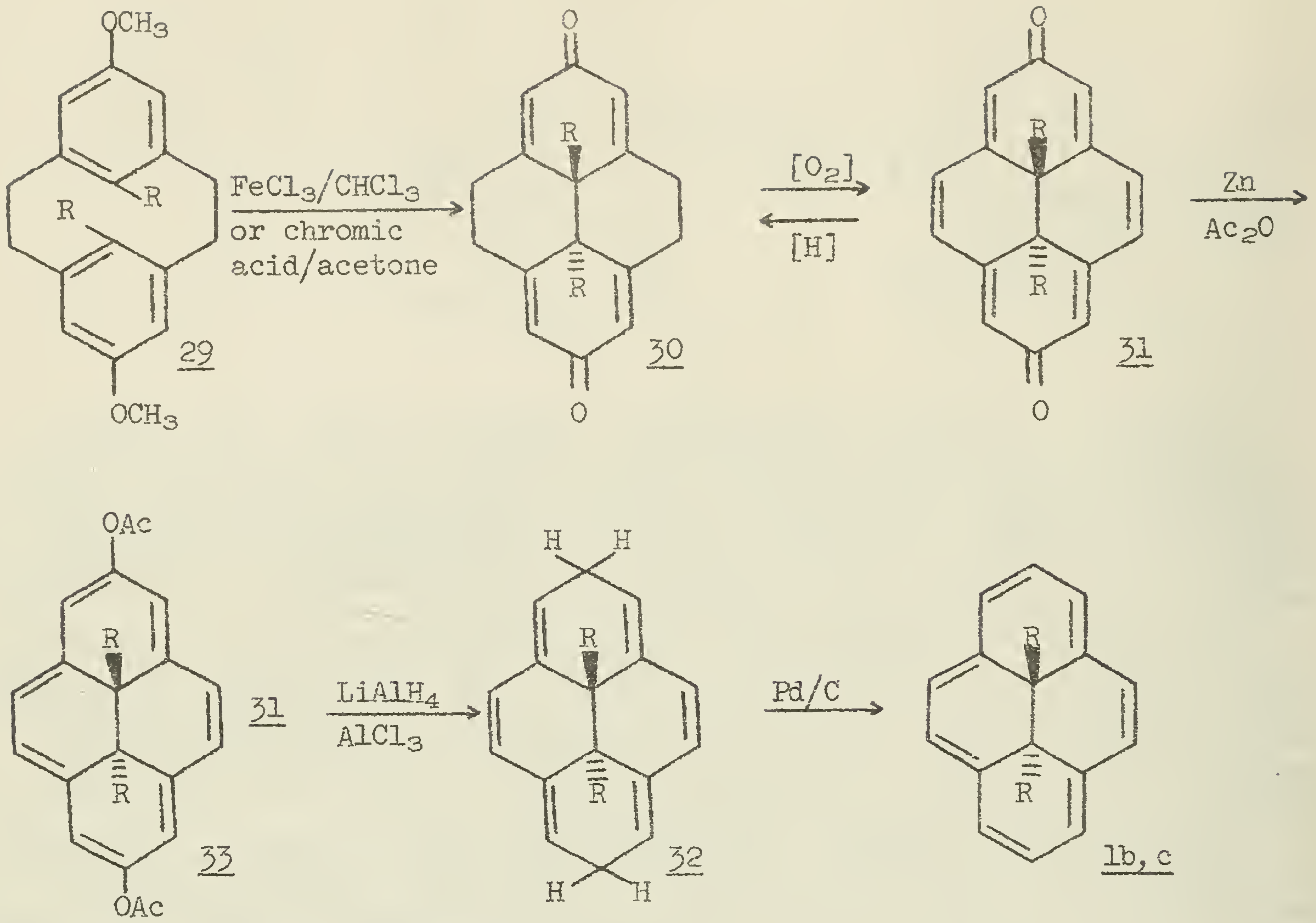


Treatment of 13b with $(MeO)_2\overset{+}{C}HBF_4^-$, followed by NaH in THF, gave the corresponding cis-metacyclophane, the first known of this geometry. The cis and trans forms are readily distinguishable by their nmr, as the internal methyl of the trans form appears at τ 9.0-9.5, an upfield shift from the normal value of toluene of 1.5 ppm due to the ring current in the neighboring benzene, while the cis-metacyclophane shows no such effect.

The synthesis of trans-15,16-dialkyldihydropyrenes was also accomplished by introduction of the central 15,16 bond into the metacyclophane at an earlier stage. A modification of syntheses of trans-15,16-dimethyldihydropyrene[12-14] and the diethyl analog[15] allowed the development of a method with general application.[16] Thereby, consequences of having a larger group substituent in the pi-electron cloud could be investigated.

It was initially thought that 29 would have to be cleaved to the phenol to undergo phenolic oxidation-radical coupling to the dienone 30, and it was surprising that this coupling occurred with the phenolic ether 29. Studies have not yet shown whether this is a general procedure.





PHYSICAL AND CHEMICAL PROPERTIES

The trans-15,16-dialkyldihydropyrenes exist as emerald green crystals. The ultraviolet spectra of the dimethyl-1(1b) and diethylhydropyrenes are in very good agreement with theoretical values predicted for a 14-pi electron system by Heilbronner.[23]

The esr of the radical-anion of 1b, formed by reduction with sodium or calcium in 1,2-dimethoxyethane, and the radical-cation of 1b, formed by solution of 1b in concentrated sulfuric acid, were taken and the coupling constants (designated "a") are summarized in figure 34.[24] Perturbation theory requires that the unpaired electron in the radical-anion be placed in the lowest antibonding orbital. However, Heilbronner's measurements[24] show that this electron is actually in the higher bonding orbital. It is also interesting that the coupling constant $a^{-}_{CH_3}$ for the radical-anion of 1b is twice as large as the corresponding constant $a^{+}_{CH_3}$ in the radical-cation. This contradicts existing knowledge that such coupling constants are about twice as large in the cation as in the corresponding anion in the radical ion of an aromatic, alkyl-substituted system. Heilbronner's explanation for this is that the perturbation of the CH_3-C(15)-C(16)-CH_3 "butane" unit depends on the absolute charge of the substituted center. In other words, the "butane" unit acts as an electron accepting group in the radical-anion, but as an electron releasing group in the radical-cation. This reversal of electronegativity is attributed to a hyperconjugative rather than an inductive effect, since an attractive inductive effect would not be great enough to decrease the large electron supply at the sp^2 center at the perturbed carbons 11, 12, 13 and 14.

The nmr spectra[14-16] of the dihydropyrenes, as summarized in Table I,[11,25] are particularly interesting. They show the presence of a strong induced ring current, as would be expected for an aromatic molecule. The internal substituents are shifted to a very high field, while peripheral protons appear

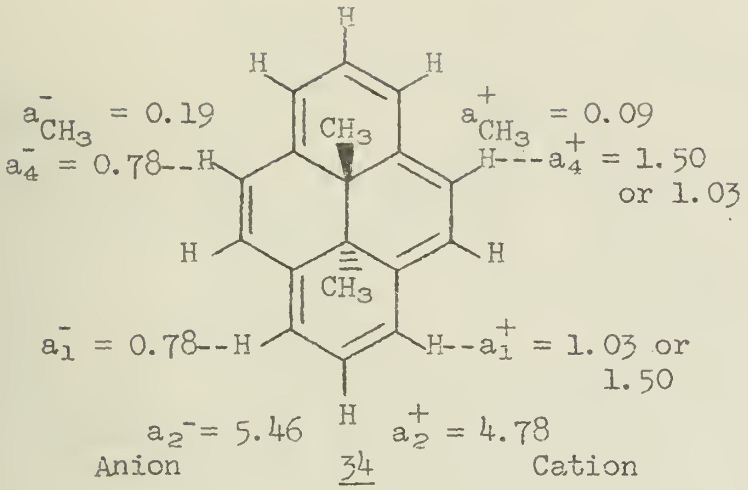


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Table I

R	Chemical shifts, τ Protons of the interior alkyl groups α	β	γ	Exterior protons
	Neutral Hydrocarbons			
H	(15.49)			1.42-2.11
$\overset{\alpha}{CH_3}$	14.25			1.33-2.05
$\overset{\alpha}{CH_2}\overset{\beta}{CH_3}$	13.96	11.86		1.33-2.05
$\overset{\alpha}{CH_2}\overset{\beta}{CH_2}\overset{\gamma}{CH_3}$	13.95	11.87	10.65	1.33-2.05
	Dianions			
$\overset{\alpha}{CH_3}$	-11.00			13.19-13.96
$\overset{\alpha}{CH_2}\overset{\beta}{CH_3}$	-11.15	-0.70		12.50-13.14
$\overset{\alpha}{CH_2}\overset{\beta}{CH_2}\overset{\gamma}{CH_3}$	-11.24	-2.59	+4.49	12.56-13.14

downfield below the normal region for benzene protons. As the internal alkyl group is lengthened from methyl to ethyl to n-propyl, it extends further through the cavity of the pi cloud and the proton resonances of these substituents provide a mapping of the magnetic effects due to ring current. It can be seen that the diamagnetic ring current shielding effect decreases as the internal protons become more distant from the ring. When these molecules are converted to their dianions, by reduction with sodium or calcium in 1,2-dimethoxyethane, there is a change from an aromatic 4n + 2 system to an antiaromatic 4n system. The nmr spectra show a dramatic reversal in ring current effects, indicating a strong paramagnetic ring current effect[26] in the three dianions. Similar results have been reported by Oth for (16)annulene[27] for the corresponding dianion.[28]

X-ray crystallographic studies show that 2,7-diacetoxy-trans-15,16-dimethyldihydropyrene (33)[29] is nearly planar and has bond lengths comparable to benzene. The same is true of trans-15,16-diethyldihydropyrene (1c),[30] which has a slightly larger deviation from the mean plane. These compounds are aromatic in the classic sense, as they undergo electrophilic substitution rather than addition. The dimethyl-,[14,31] diethyl-,[15] and di-n-propyldihydropyrenes[16] are nitrated by stirring with cupric nitrate in acetic anhydride in 99%, 53%, and 58% yields. Nitration occurs at the 2 position, which has the highest electron density. The chemical properties of 1b have been extensively studied,[14,31] and this molecules undergoes further substitution reactions at the 2 position of deuteration, bromination, Friedel-Crafts acylation, and formylation. Hydrogenation and Birch reductions have also been done.

From the evidence, it is clear that the trans-15,16-dihydropyrenes meet the requirements for aromaticity, and that it is possible to place substituents reaching into the cavity of the pi-electron cloud.

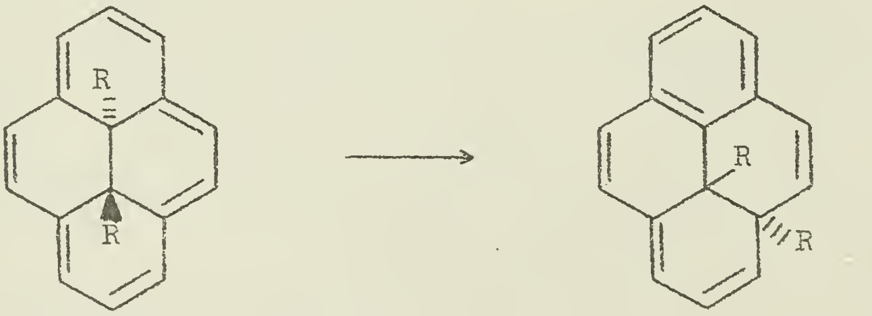
PHOTOCHEMICAL AND THERMAL ISOMERIZATIONS

The nmr spectra show that the trans-15,16-dialkyldihydropyrene structure (1) is preferred over the valence tautomer, the (2.2)metacyclophane-1,9-diene (3). However, all alkyl derivatives (1) undergo photoisomerization to their corresponding (2.2)metacyclophane-1,9-diene tautomers (3).[14,16,32] The reaction is reversed in the dark. The reactions can be followed by nmr, since the internal alkyl group (e.g., CH_3) is shifted from τ 14.20 to τ 8.48, the normal range for an interior metacyclophane methyl, as the reaction proceeds. The dark reaction follows first order kinetics, and the rate is temperature dependent. An electron-attracting substituent in the 2- or 7-position greatly enhances the rate of the dark reaction.

The trans-15,16-dihydropyrenes undergo an interesting thermal isomerization, involving migration of one of the alkyl groups to the periphery.[15, 16, 33] The temperature required for thermal isomerization of trans-15,16-dimethyldihydropyrene 16 is 190-210°,[15] but both trans-15,16-diethyldihydropyrene 1c and trans-15,16-di-n-propyl dihydropyrene are readily isomerized in boiling cyclohexane.[33] The mechanism has not been established, but it is probably a 1,5-sigmatropic shift of the alkyl group or two successive 1,2 alkyl shifts. The structures of 35a-d are supported by their nmr spectra. The rearranged dimethyl compound 35b exhibits a multiplet centered at 3.10 (3 H, ArH), a complex multiplet at 3.55-4.30 (7 H, -CH=C-), a singlet at 8.63 (3 H, CH_3), and a singlet at 8.87 (3 H, CH_3).[33] Elemental analysis proved that the rearranged products were isomeric with starting materials (1a-d), and loss of the dihydropyrene system was shown by disappearance of the emerald green color and of the very high field shifts for the interior alkyl groups. Further proof of structure came from hydrogenation products of 35b, which showed the predicted nmr and mass spectra.

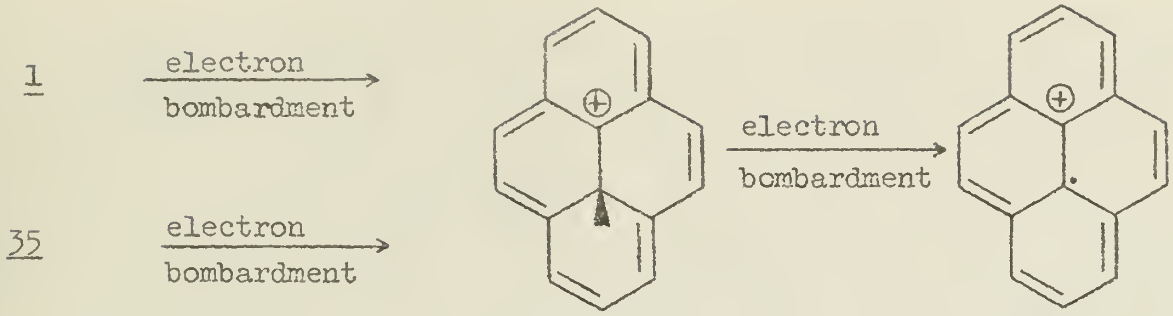
The mass spectra of compounds 1a-d and their corresponding isomerization products 35a-d are essentially the same. They show small parent ion peaks, much stronger peaks for loss of one alkyl group, and still stronger peaks for the loss of both alkyl groups, with further fragmentation corresponding to that of pyrene. This similarity in spectra can be rationalized if the first fragmentation of 35 is loss of the peripheral alkyl group.

Since Heilbronner's studies had indicated methyl hyperconjugation at the 15 and 16 positions, the possibility of methyl interchange at the temperature required for thermal rearrangement was considered. Thermal isomerization of optically active 4-carboxy-trans-15,16-dimethyldihydropyrene (38)[33] showed that this interchange did not occur. The reaction was followed by examining the visable region, where 38 absorbs but the thermal rearrangement preducts do not. A solution of 38 was heated and a comparison of the visable absorption bands before and after heating showed that 47% of 38 still remained. The optical rotatory dispersion curve of this resulting solution in the visable region corresponded exactly in overall shape to that of 38, with a decrease in the specific rotation of the various peaks and troughs of 53%. Methyl interchange would have led to a racemic mixture, which was not observed.



1a-d

35a, R = H
b, R = CH_3
c, R = C_2H_5
d, R = C_3H_7



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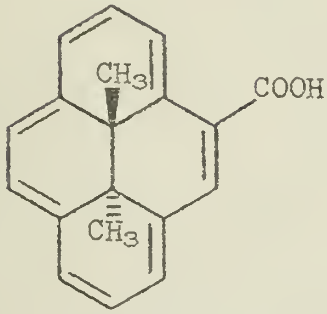
CIS-15,16-DIHYDROPYRENES



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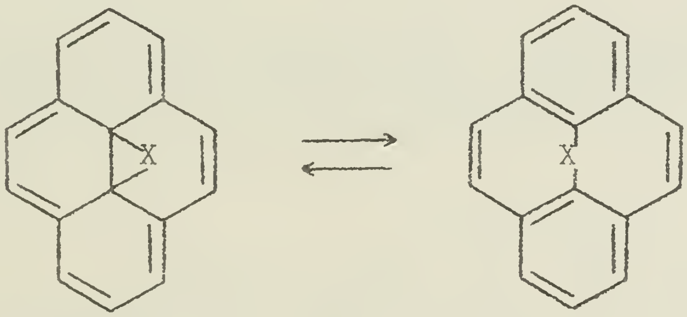
The main work on the dihydropyrenes has involved compounds with *trans* substitution at the 15 and 16 positions, since the key intermediate in the synthesis is a metacyclophane. As was mentioned earlier, metacyclophanes exist as the *trans* isomer,[3] and there is no conversion to the *cis* isomer up to 190°.[34] An alternative approach to the *cis*-15,16-dihydropyrenes was developed, involving the presence of an additional three-membered ring bridging the 15 and 16 positions. Syntheses towards the epoxide (39a),[35,36] aziridine (39b),[37] and cyclopropane (39c)[38a,b] derivatives were directed through their valence tautomers (40a-c). However, in contrast to the *trans*-15,16-dihydropyrenes, the spectral evidence showed that of the valence tautomers the *cis*-(2.2)-metacyclophane-1,9-diene (40a-c) predominated at room temperature. The synthesis of *cis*-8,16-oxido(2.2)metacyclophane-1,9-diene 39a is outlined.

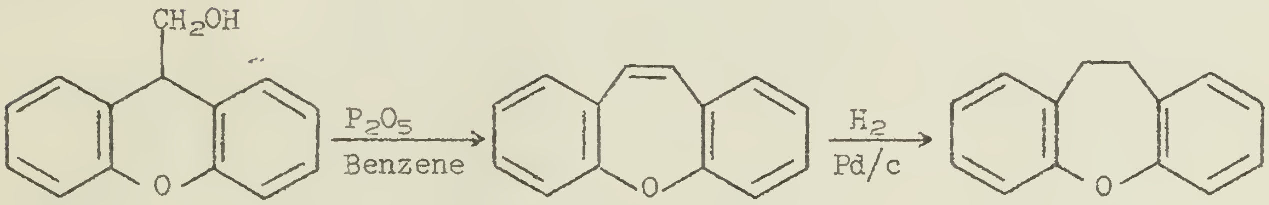
It is of interest that a solution of 40 in trifluoroacetic acid gave a slowly fading green color. This has been attributed to the *cis*-dihydropyrene (49) or to (50), which further reacts to give pyrene (51) and trifluoroperacetic acid.



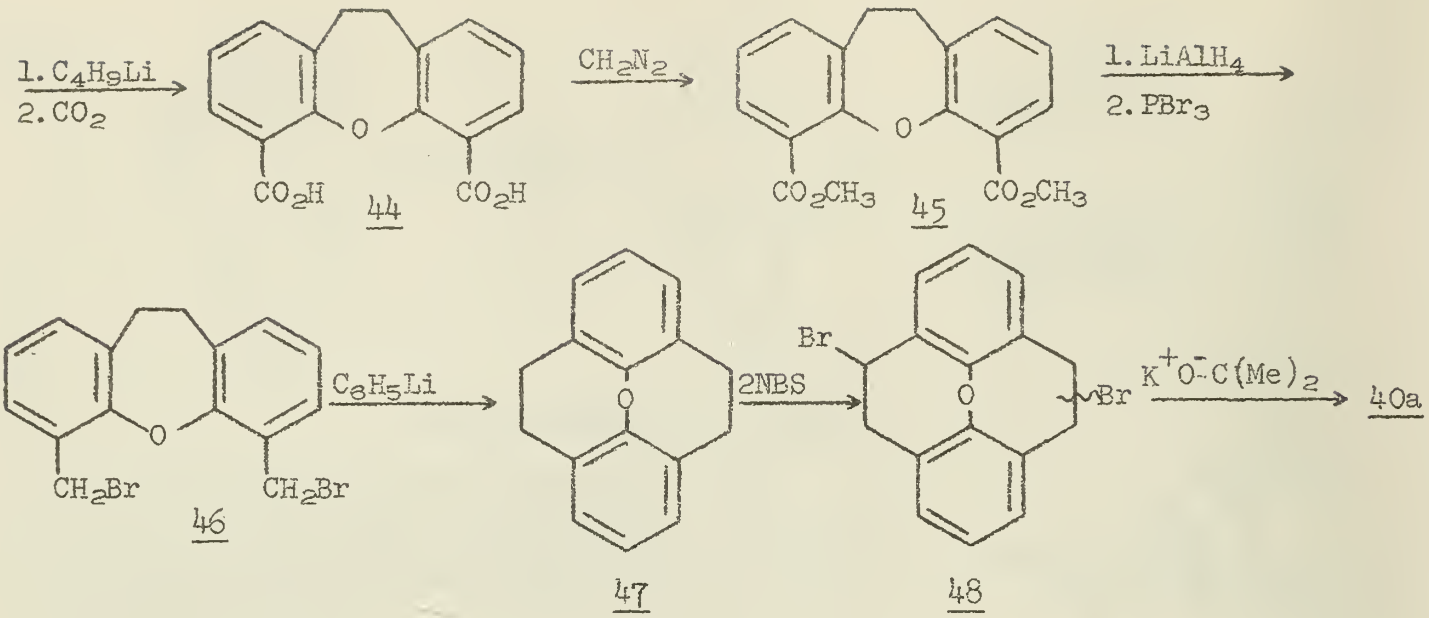
39a, X = O
b, X = NH
c, X = CH_2

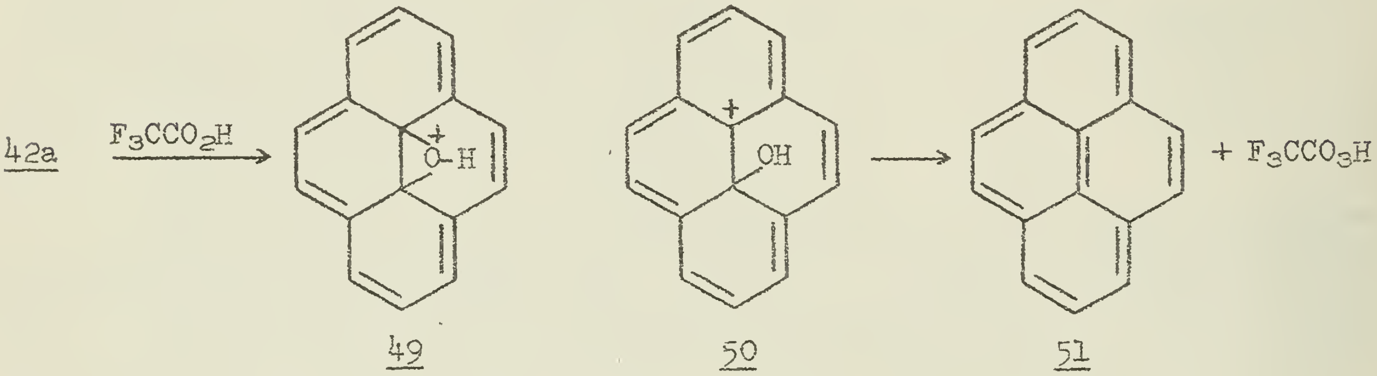
40a, X = O
b, X = NH
c, X = CH_2

Synthesis:



41 42 43





CONCLUSION

The trans-15,16-dihydropyrenes are a new class of compounds whose properties meet the requirements for aromaticity. They show that it is possible to have an alkyl group substituent extending through the pi-electron cloud, and it will be interesting to see if the effects of other than alkyl substituents will be studied in the future.

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UV IRRADIATION OF PESTICIDES

Reported by Alan Morrice October 12, 1970

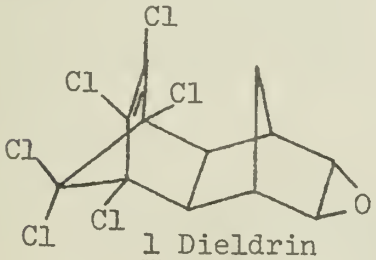
INTRODUCTION

The effect of sunlight and artificial light on pesticides has received much attention recently. Rightly so, since any alteration of pesticides under field conditions is of interest as it may affect their activity, toxicity, and eventual fate. The finding of build-up of, e.g., DDT, in animal tissues also requires that some potential method for the destruction of these compounds be found. This topic has recently been the subject of two reviews.[1,2] For more general information on the degradation and effects of herbicides and pesticides on the environment see Kearney[3] and the A.C.S. report, "Cleaning our Environment; The Chemical Basis for Action."[4] It is the intention of this seminar to cover recent work on this topic since these reviews appeared.

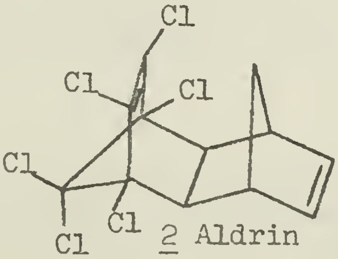
DIELDRIN AND ALDRIN

Dieldrin and Aldrin are shown in structures 1 and 2. Rosen and Sutherland[5] found that a solid sample of Aldrin exposed to sunlight for one month gave a mixture having the following composition: 4.1% 1, 2.6% 2, 24.1% 4, and 59.7% polymer. The polymer was insoluble in all of the solvents used (hexane, hexane/ethyl acetate were specifically mentioned) and remained behind on the glpc column employed to isolate the other products. If there has been build-up of this polymeric material in the environment, then it has easily escaped detection and its further action is also unknown. Rosen and Sutherland found the relatively fast photolysis surprising since Aldrin has an absorption maximum at 215 nm and it is believed that all sunlight of wavelenth less than 290 nm is absorbed by the atmosphere.[6]

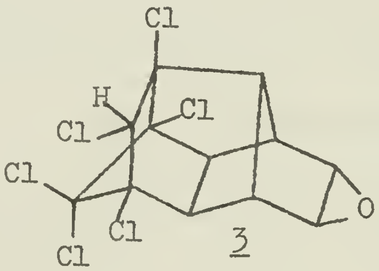
Henderson and Crosby,[7] using separate solutions of Dieldrin and Aldrin in hexane, cyclohexane, and methanol, and irradiation at 253.7 nm obtained a single degradation product from each in significant quantity, which they identified as 5 and 6 respectively. Examination of solutions in the above solvents irradiated at wavelengths between 250 nm and 300 nm showed maximum conversion of 1 to 5 at 250 nm and none above 260 nm. No trace of 3 could be obtained by irradiation between 250 nm and 300 nm, although later work by the same two authors on trace amounts of Dieldrin suspended in water and exposed to sunlight showed that Dieldrin could be photolysed to form 3 in good yield.[8] Henderson and Crosby[7] Also found 3 to be four times more toxic in mice than either Dieldrin or Aldrin, and 5 to be five times more toxic than Dieldrin.



1 Dieldrin



2 Aldrin



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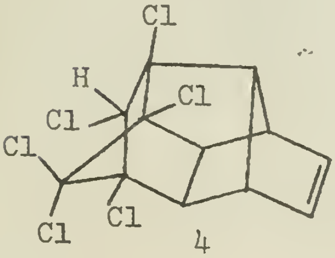

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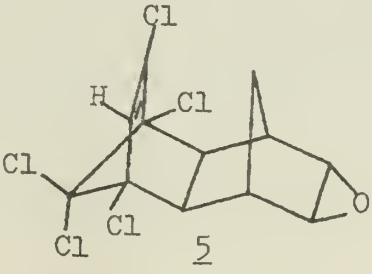

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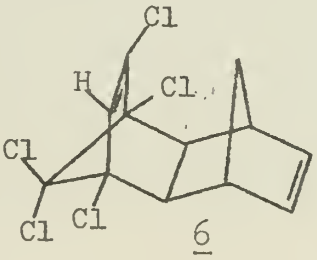

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CHLOROBENZOIC ACIDS

Plimmer and Hummer[9] irradiated methanolic solutions of 2,3,6-trichlorobenzoic acid under nitrogen and obtained a mixture of benzoic, m-chlorobenzoic, 2,5-, and 2,6-dichlorobenzoic acids. Irradiation of Amiben (3-amino-2,5-dichlorobenzoic acid) and its methyl esters by the same workers at wavelengths greater than 280 nm under conditions in which oxidation was prevented gave selective loss of the 2-chlorine with the formation of 3-amino-5-chlorobenzoates.[10] Irradiation in the presence of air or oxygen afforded a complex mixture of oxidation products, later confirmed by Crosby and Leitis.[11] A free radical mechanism was postulated by analogy with earlier work done by Joschek and Miller[12] on similar compounds. Although some replacement of the chlorine by hydroxyl would have been expected, they suggested the aminophenol thus formed may have polymerized or may have been oxidized during subsequent manipulation. They concluded that photochemical loss of halogen from an aromatic ring proceeded by a free radical mechanism, the products depending on the environment of the molecule. Reductive dechlorination took place in hydrogen-donor solvents such as alcohols, hydrogen abstraction taking place preferentially from the α-position. Phenylation occured in benzene. Loss of chlorine from o-chlorobenzoic acid was more rapid than loss from the m- and p-isomers, and with multichlorinated compounds preferred loss of certain chlorine atoms occured, the ease of loss depending on the orientation of the ring substituent.

Crosby and Leitis[11] irradiated aqueous solutions of 2-, 3-, and 4-chlorobenzoic acids at 253.7 nm for up to three hours and in sunlight for up to fourteen days and, as well as replacement of chlorine by hydroxyl and hydrogen, obtained 4-acetylbenzoic acid and terephthalic acid in very much smaller amounts. The terephthalic acid was suggested as being derived from reaction of the aromatic halogen compound with carbonate ion from the surrounding medium, presumably by some kind of an ionic displacement mechanism, although the authors did not venture a statement. They did suggest that the failure to detect chlorobenzene, 4,4'-dichlorobiphenyl, biphenyl-4,4'-dicarboxylic acid, and other products expected from a free radical mechanism, may have been due to the high dilution involved, or, perhaps, to an ionic mechanism although no analogies with other work are given. In sunlight the monochlorobenzoic acids remained unaffected. They found the fact that at alkaline pH the reduction product (benzoic acid) represented at least 90% of the total photolysate of 4-chlorobenzoic acid and appeared to be stable to further photolysis in contrast to the work of Joschek and Grossweiner,[13] who showed that radicals were produced by acids of this type. They concluded that when multiple chlorines were present, replacement of either or both halogens by hydroxyl or hydrogen was to be expected and formation of polyhydric phenols in this way would finally lead to polymer formation similar to that of 2,4-D.

CHLOROPHENYLACETIC ACIDS

The herbicide Fenac is a mixture of chlorinated phenylacetic acids in which the 2,3,6-trichloro isomer predominates. Irradiation of aqueous solutions of Fenac in sunlight and at 254 nm afforded complex mixtures.[14] Use of the isomeric monochlorophenylacetic acids led to the postulated pathway given in Fig. 1. Hence, by analogy, the pathway given in Fig. 2 was postulated as being a possible decomposition pathway for Fenac. It was recognized that other intermediates possibly occur.

Although the photolysis of Fenac in sunlight is extremely slow, it may be anticipated that sufficiently long term irradiation could result primarily in benzoic acid and humic acid polymers.

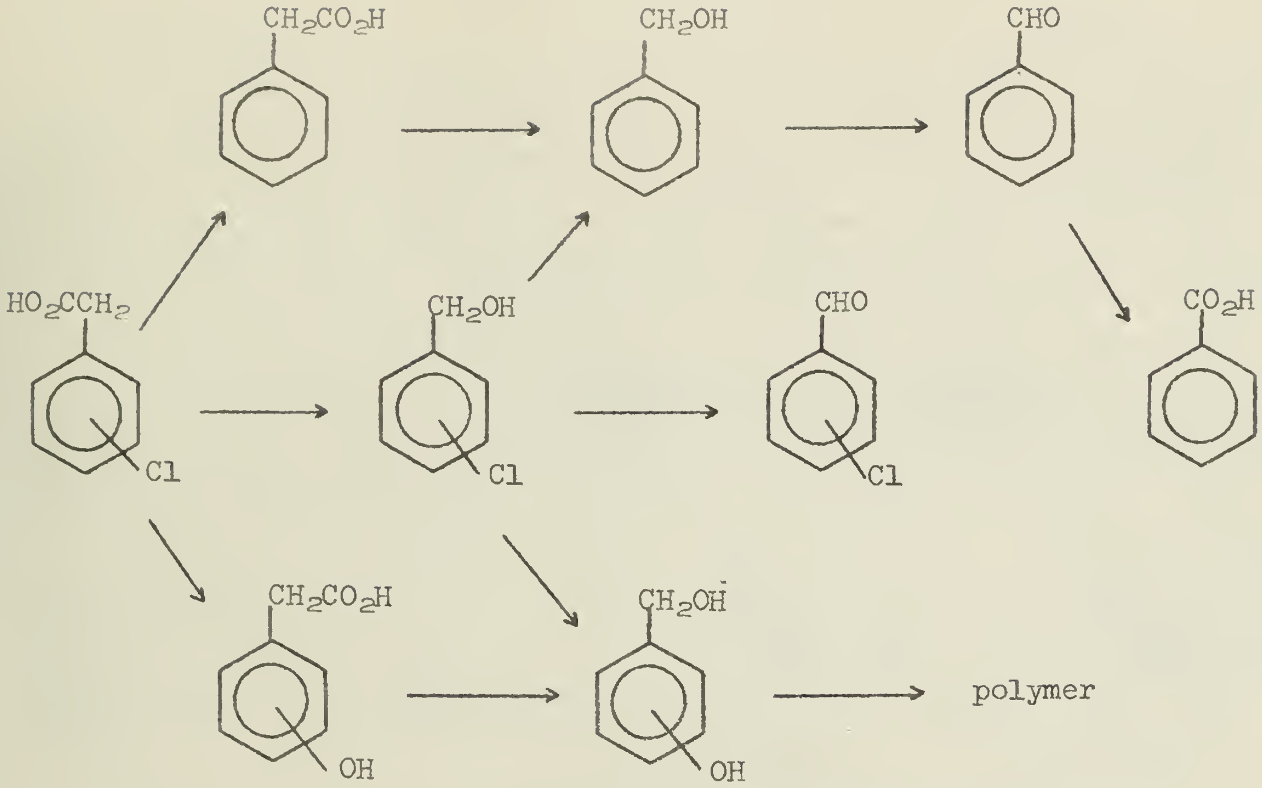


Fig. 1. Decomposition of Monochlorophenylacetic Acids

1-NAPHTHALENEACETIC ACID (NAA)

NAA, in the form of ammonium or alkali-metal salts, is a plant-growth regulator. Luckwill and Lloyd-Jones[15] demonstrated its photodecarboxylation when exposed to sunlight either as a solid or in aqueous solution. Watkins and Woodcock[16] found, on irradiation of a 5% ethanolic solution of NAA in the presence of air at 253.7 nm for seven days four major and seventeen minor products of decomposition. There were able to identify ethyl 1-naththoate, 1-naphthoic acid, naphthalene, 1-methylnaphthalene, and phthalic acid. Later work[17] showed that on irradiation of aqueous solutions, 1-naphthaldehyde, 1-naphthylcarbinol, 1-naphthoic acid, 1-methylnaphthalene, and naphthalene could be identified. Irradiation of ethanolic solutions gave in addition ethyl 1-naphthylacetate. 1-Naphthoic acid was judged to have originated by aerial oxidation of 1-naphthaldehyde. A free radical mechanism was suggested, with naphthalene and 1-methylnaphthalene arising by simple decarboxylation to a radical which could then abstract hydrogen presumably from the solvent. Crosby and Tang[18] obtained similar results using aqueous solutions and on the basis of these also postulated a free radical mechanism for the following reasons: (1) under nitrogen, formation of 1-methylnaphthalene was essentially pH independent; (2) NAA, λ^{o}_{max} 272, 282, 292 (shoulder) nm, can absorb so little energy from sunlight that the rapid formation of 1-methylnaphthalene via an ionic intermediate would not be expected. Absorption of energy for a radical intermediate, however, could take place at much longer wavelengths; (3) removal of photolysis products as they were formed showed that 1-methylnaphthalene was produced rapidly in nitrogen; the reaction was slow in air, the short term products being only 1-methylnaphthalene, 1-naphthylcarbinol, and phthalic acid in approximate ratio of 1:10:30. An ionic mechanism does have some basis due to work by Margerum[19] on nitrophenylacetates. The pathway postulated by Crosby and Tang is given in Fig. 3.

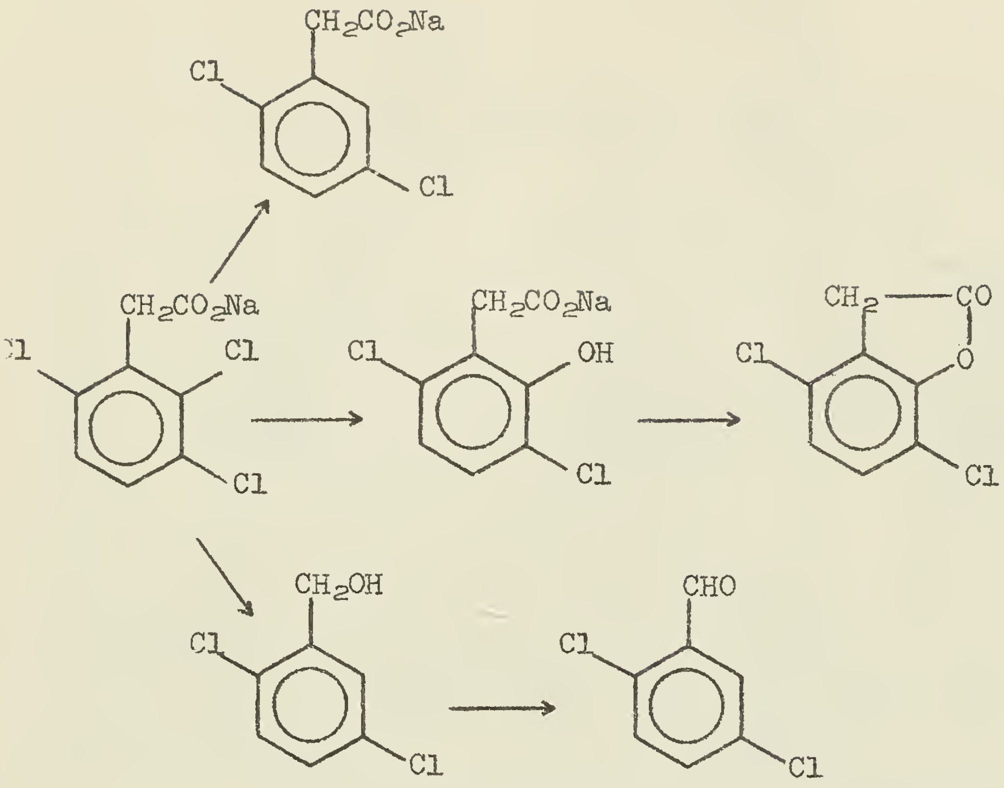


Fig. 2. Decomposition of Fenac

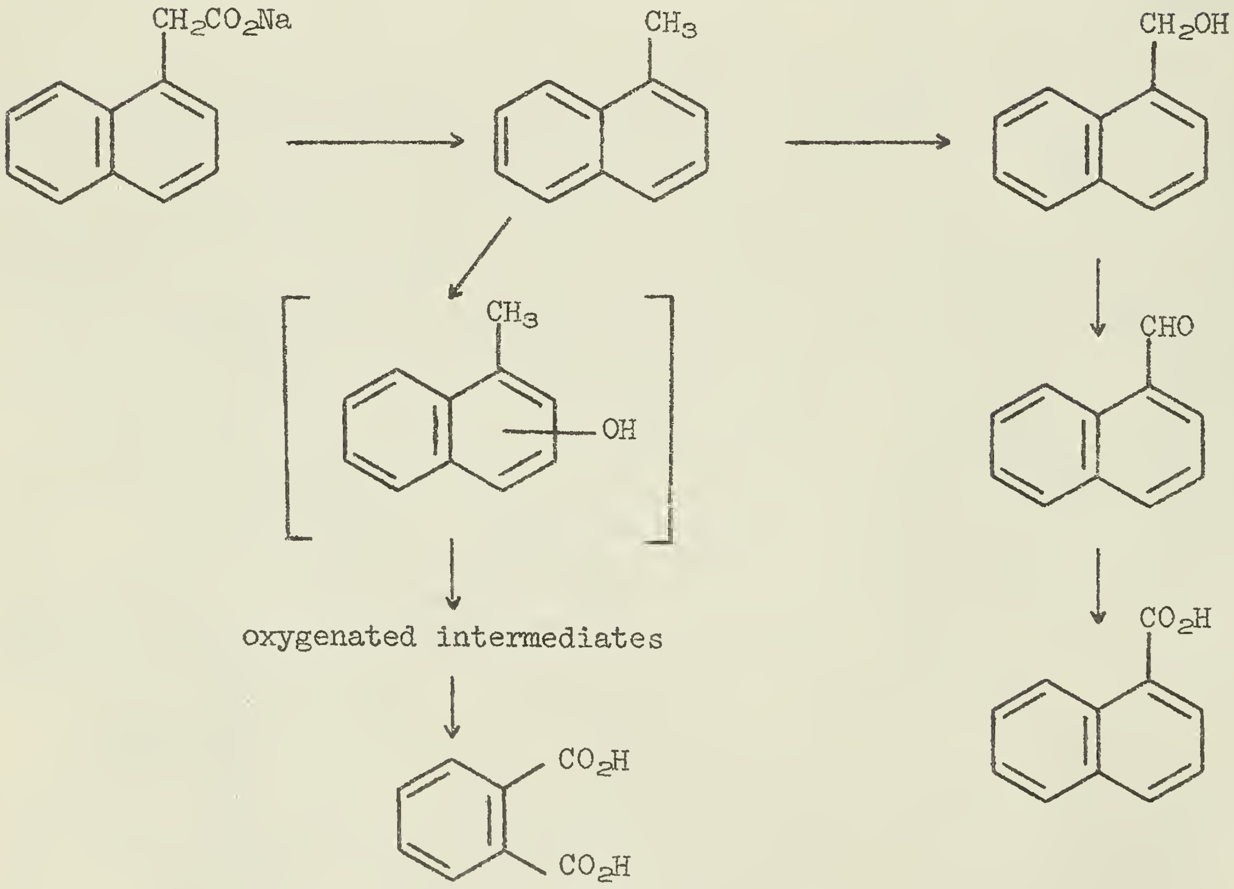


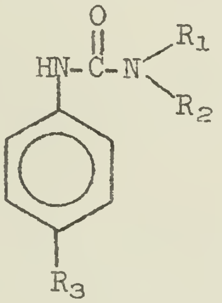
Fig. 3. Decomposition of NAA

UREA HERBICIDES

3-(p-Bromophenyl)-1-methoxy-1-methylurea (7) was used as a model compound for this class of herbicides.[20] Exposure to sunlight in aqueous solution gave rise to the major product 8, minor products 9 and 10, and an unidentified compound 11, possibly dimeric. No evidence of 3-(p-bromophenyl-1-methoxyurea (12) could be found, implying that demethoxylation occurred in preference to demethylation. The exposures were done in solution in the presence of air. Compound 11 was thought to be formed by dimerization of 7 accompanied by loss of HBr.

A study of the effect of sunlight on aqueous solutions of Monuron (13) in the presence of air showed that decomposition amounted to less than 6 in fourteen days.[21] The breakdown pattern was not particularly dependent on initial Monuron concentrations, solutions containing either 200 ppm or 20 ppm produced the same decomposition products, summarized in Fig. 4.

In similar experiments in aqueous solution, Rosen, Strusz, and Still[22] found the phenol 14 in addition to the other products. They also studied the photodecomposition of Linuron 15, and Metobromuron 16. Their results are given in Figs. 5 and 6. It is of interest that γ-irradiation of substituted aromatic compounds in dilute aqueous solution also yields hydroxylated products by a free radical mechanism.[23]



	R_1	R_2	R_3
7	Me	OMe	Br
8	Me	OMe	OH
9	Me	H	Br
10	H	H	Br
12	H	OMe	Br

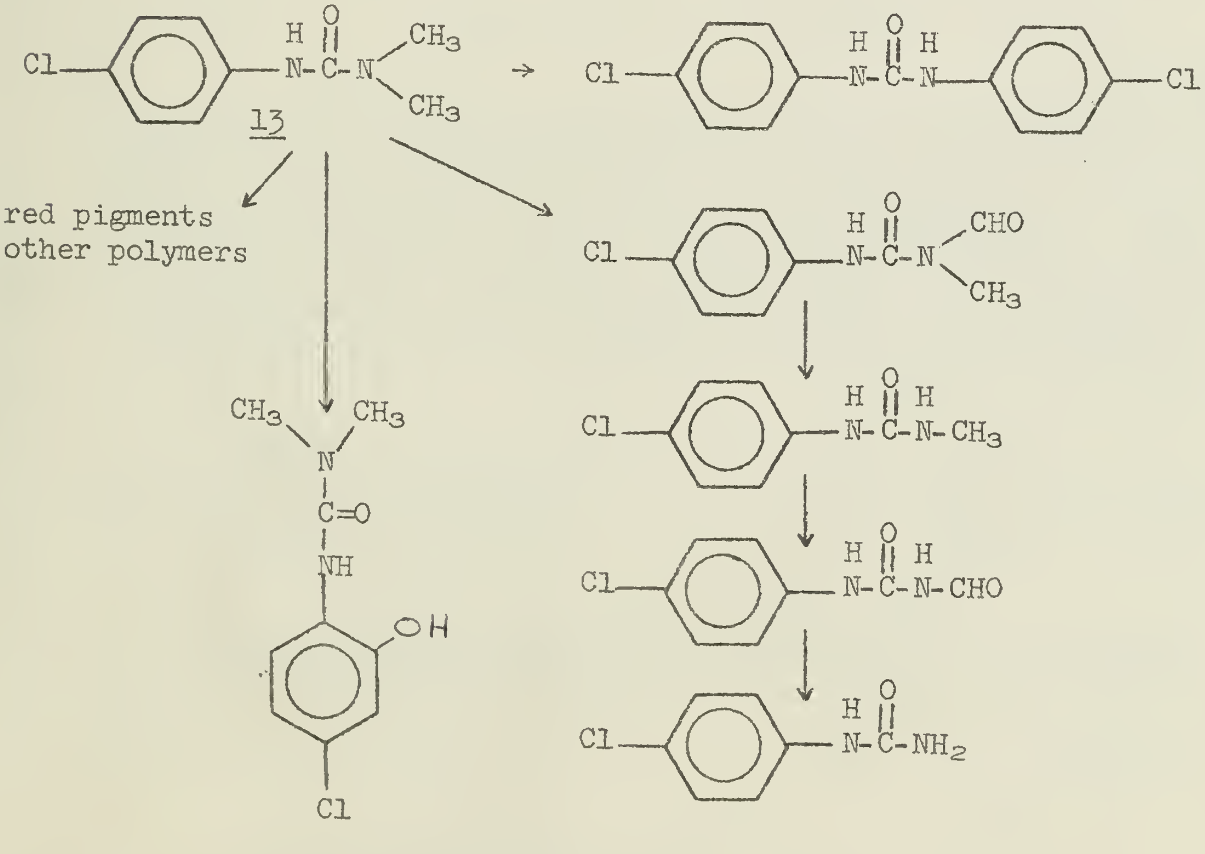
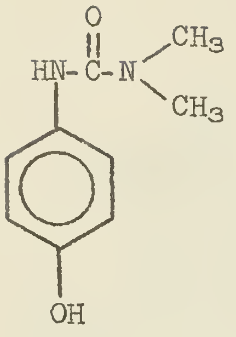


Fig. 4. Decomposition of Monuron



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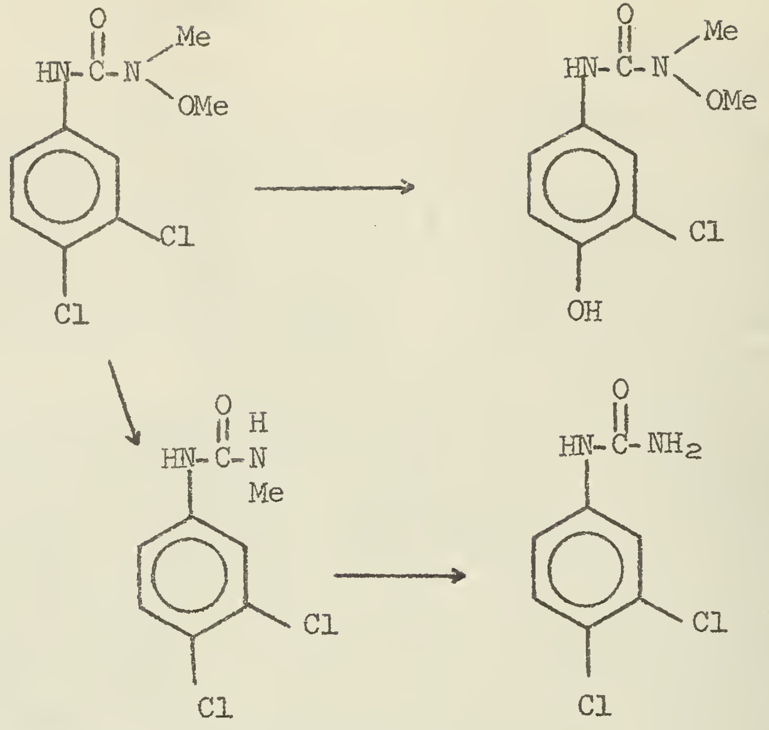

Fig. 5. Decomposition of Linuron

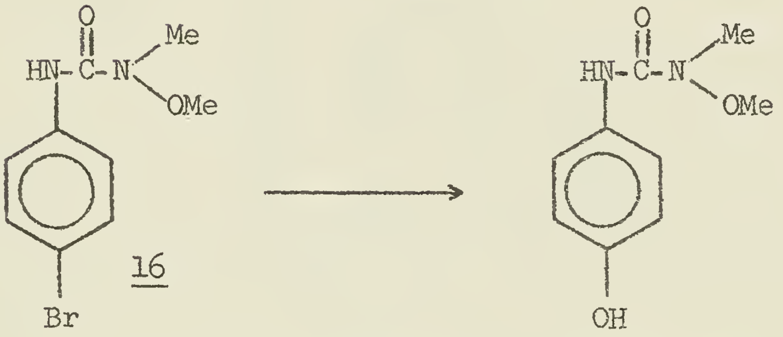

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Fig. 6. Decomposition of Metobromuron

METHYL CARBAMATES

The photodecomposition of 4-dimethylamino-3,5-xylyl methylcarbamate (Zectran, 17) and 4-dimethylamino-3-cresyl methylcarbamate (Matacil, 18) as deposits on bean foliage studied by Abdel-Wahab and Casida[24] was found to involve only the ~~carbamate~~ dimethylamino moiety (Fig. 7). The order of decreasing toxicity within each series when piperonyl butoxide is used as synergist is as follows; dimethylamino > methylformamido > formamido > methylamino > amino. No attempt was made to give a mechanism and it is possible that more than one is in operation.[25]

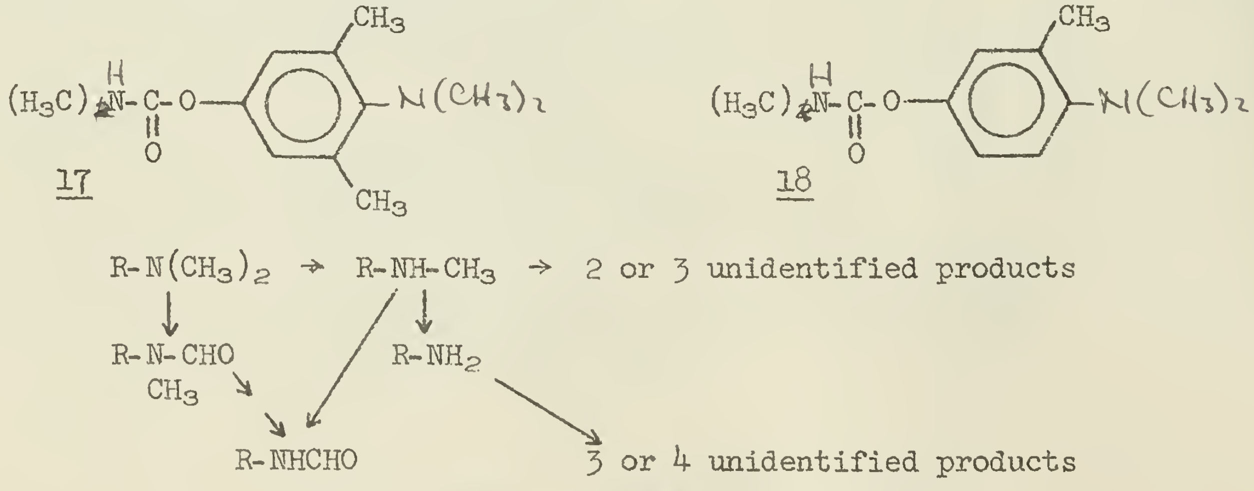

Fig. 7. Decomposition of Matacil and Zectran

SUMMARY

The photolysis of pesticides leads often to complex mixtures of oxidation products. In many cases the mechanisms are not known and although sensitization is of the greatest significance in irradiation experiments both in the laboratory and in the field our knowledge of this is slight in the case of herbicidal compounds. A more extended discussion of this is given in the review by Crosby.[2] In a few cases criteria for free radical mechanisms exist but a complete knowledge of even these is still lacking, e.g., in the extent of involvement of oxygen, or whether singlet or triplet states are involved. It appears both reasonable and probably that in many cases photolysis will provide the same products as metabolism by plants and microorganisms. Consequently it may be difficult to demonstrate clearly that a particular plant metabolite did not arise from both sources in the field. Such studies, however, are necessary if we are to know the fate of such compounds in our environment and to formulate possible procedures for their destruction.

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TRANSANNULAR REACTIONS IN CARBOCYCLIC SYSTEMS

Reported by James R. Ghesquiere October 15, 1970

INTRODUCTION

Transannular reactions[1] are chemical transformations which involve the formation of a full bond between atoms on the opposite sides of the ring and which normally do not proceed in open chain systems. These reactions may proceed through different types of intermediates. There are reports of transannular reactions in medium-sized (8-11 carbon atoms in the ring) carbocyclic rings involving free radicals, carbenes, carbanions, and carbonium ions. This seminar will be limited to transannular reactions in medium-sized carbocyclic rings proceeding through carbonium ions, which are a result of solvolysis, and to carbene transannular reactions.

TRANSANNULAR REACTIONS DURING SOLVOLYSIS

Considerable interest in transannular reactions was generated by the discovery that a transannular hydride shift competes effectively with a nucleophilic solvent for a carbonium ion in a medium-sized ring.[2,3] During a solvolysis experiment in a medium-sized ring many factors may affect the formation of a cationic center. The formation of the carbonium ion center may be assisted by a π bond or a cyclopropane ring located on the opposite side of a medium-sized ring. Whether a transannular reaction will occur is also affected by substituents on the ring and the rigidity of the medium-sized ring.

The eight-membered ring has been the most studied for occurrence of transannular reactions. Much of the early work was done by Cope[4-6] on *cis*-cyclooctene oxide (1), and recent work has been done on a symmetrically bridged cyclooctane ring, *exo*-2,3-epoxybicyclo[3.3.1]nonane (2).[7,8]

The formolysis of 1 (Scheme 1) was found to give four products, three of which (3, 4, 5) involved a transannular hydride shift. By means of a degradative study on deuterium labeled compounds, Cope established that a 1,5-hydride shift accounted for 61% of the transannular products and that a 1,3-hydride shift accounted for 39% of the transannular products.

However, when the solvent medium was changed, 1 gave different product distributions. The various solvents used are listed in Table 1. The solvolysis of 1 in trifluroracetic acid resulted in only transannular products. At the other extreme, an acetic acid solution buffered with sodium acetate gave only 24% of transannular reaction products and 76% of normal products. The remaining solvents studied resulted in product mixtures between these two extremes. The products obtained in all of the solvolyses are given in Scheme 1.

The solvolysis of 2 in buffered acetic acid at 100° for 72 hours yielded a mixture of ene-ol and diol fractions (Scheme 2) after lithium aluminum hydride (LAH)reduction of the initial acetate adduct.[8] The products which result from transannular reaction are 7-bicyclo[3.3.1]nonen-*exo*-2-ol (7), 6-bicyclo[3.3.1]nonen-*exo*-2-ol (8) (7 + 8 = 23%), 7-bicyclo[3.3.1]nonene-*exo*-3-ol (9) (3%), and 7-bicyclo[3.3.1]nona-*exo*-2-*exo*-7-diol (10)(5%). The product which result from a normal reaction are bicyclo[3.3.1]non-3-en-*exo*-2-ol (11) (21%), bicyclo[3.3.1]nona-*exo*-2-*endo*-3-diol (12) (46%), and bicyclo[3.3.1]nona-*endo*-2-*exo*-3-diol (13) (2%). In considering the product distribution, some information concerning the preferred conformations of 2 can be postulated. Since diol 12 is a major product (46%), and diol 13 is a minor product (2%), the preferred conformation of the epoxide ring has the C_2-O bond axial like and the

Scheme 1

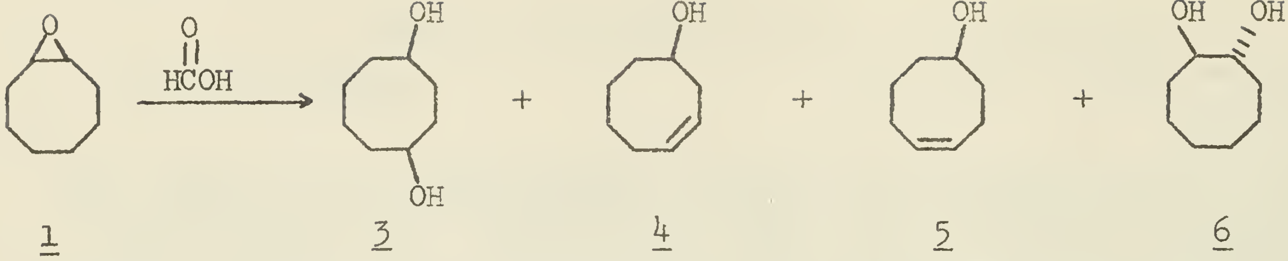
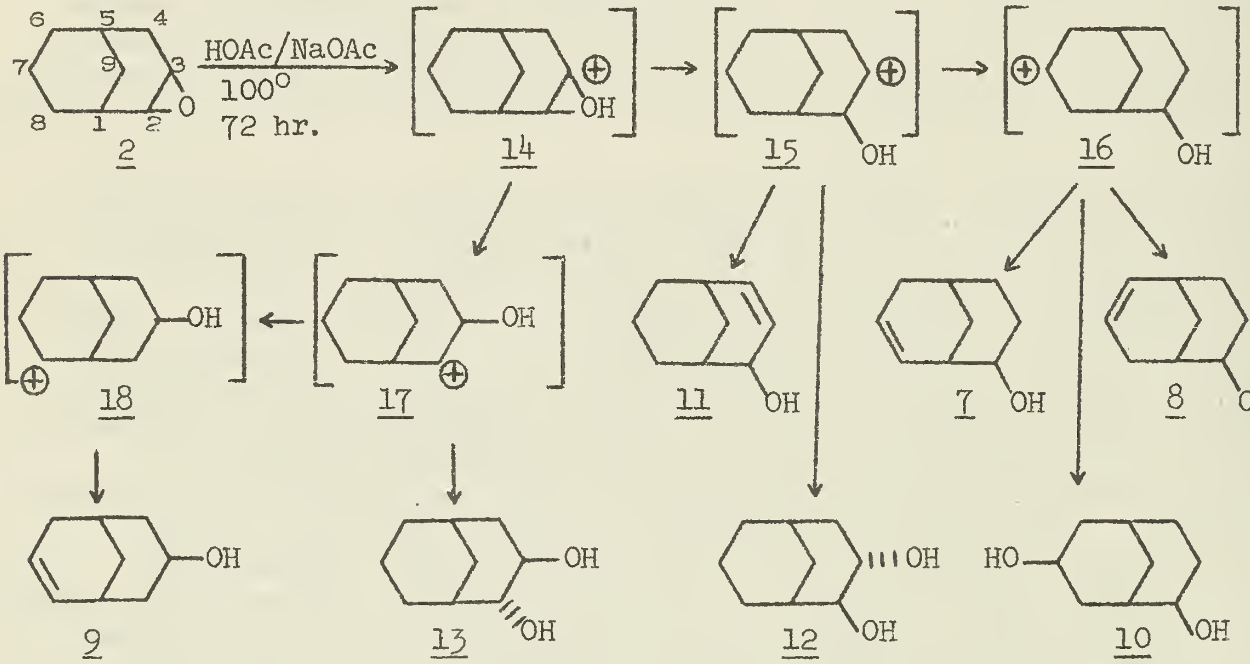


Table 1. Products from solvolysis of cis-cyclooctene oxide (1)

Acid	Normal Product, 6	Transannular Products 3	4	5	Total Yield %
Trifluoroacetic acid	0	45	34	1	80
Trichloroacetic acid	5	37	28	8	78
Formic acid	12	48	30	0	90
Acetic acid	41	21	26	2	90
Buffered Acetic acid	71	9	10	3	93

Scheme 2



C_3-O bond equatorial like (epoxide ring is opened predominately in such a way as to produce two new substituents which are trans and diaxial, rather than trans and diequatorial). The protonated epoxide (14) is converted into an intermediate carbonium ion (15). The products can be explained from the intermediate (15) by a loss of a proton at C-3 (11), by endo attack of acetate at C-3 (12), and by the formation of a new carbonium ion intermediate (16) by a 1,5-hydride shift (from C-7 to C-3). With a loss of a proton from 16 at C-6 or C-8, 7 and 8, respectively, are formed. The diol 10 is formed by exo attack of acetate on intermediate 16. The formation of 13 is explained by the opening of the protonated epoxide (14) through the non-preferred conformation, where the axial like C_2-O bond is broken, resulting in the carbonium ion intermediate (17). Endo attack on 17 by acetate ion produces 13, while a 1,3-hydride shift in 17 (from C-2 to C-8) yields intermediate 18. The final ene-ol product (9) is explained by a loss of a proton from intermediate 18.

A comparison of the solvolysis products of the monocyclic and bicyclic epoxides 1 and 2 is given in Table 2. The ratios of transannular to normal products in the two systems are very similar, with just a slight preference for the monocyclic reactant (1) to undergo transannular reactions. The bicyclic reactant (2) shows a greater tendency to give elimination products than does 1. In a comparison of the solvolysis of tosylates in related monocyclic and bicyclic series, the bicyclic reactants were found to have reduced transannular activity. These different results are thought to be a consequence of the unequally populated conformations of the related carbonium ions involved, but more complete conformational studies are desirable.[10]

Because of the transannular proximity effects in the medium-sized rings, the formation of a cationic center during solvolysis may be assisted by a π bond which is located on the opposite side of a medium-sized ring, with the formation of a new bond. The acetolysis[11,14] of the Δ^4-cycloheptenylmethyl brosylate (19) produces the cis-bicyclo[3.2.1]octyl acetate (20) by route of the (postulated) non-classical cation (21) (Scheme 3). The yield of 20 was 90% at 80° for 5 hr.

In a similar experiment, the acetolysis[12,13] of the Δ^4-cyclooct-enylmethyl tosylate (22) yielded as the major product (78%) after LAH reduction of the initially formed acetate adduct (23) the bicyclo[3.3.1]nonan-2-ol (24), and as minor products, bicyclo[3.3.1]non-2-ene (25), and after LAH reduction of 26 bicyclo[4.2.1]nonan-2-ol (27), in 14% and 7% yield, respectively (Scheme 4).

The solvolysis of Δ^3-cyclohexenylmethyl brosylate (28),[14] for which the preferred conformation of the six member ring relegates transannular interaction to a minor role, produced the 2-norbornyl acetate (30) in less than 1/2% as the only transannular product from 28 at 100° in 48 hr (Scheme 5). A control experiment demonstrated that 30 was stable to the reaction conditions. The only other product was a normal acetate substitution product 31. In considering participation of the π bond electrons in the formation of a new bond, it is found with these related examples (19, 22, and 28) that almost no participation is observed within six-membered rings, and almost 100% participation in new bond formation is observed in seven- and eight-membered rings.

The possibility of a cyclopropane ring participating in a new bond formation across a ring has been investigated in the solvolysis of various derivatives of bicyclo[5.1.0]octanols.[15] Some of the bicyclo[5.1.0]octanols have a cyclopropyl ring in close proximity to the hydroxyl group. Therefore, during the solvolysis experiment, the effect of the cyclopropyl ring on the developing carbonium center can be studied.

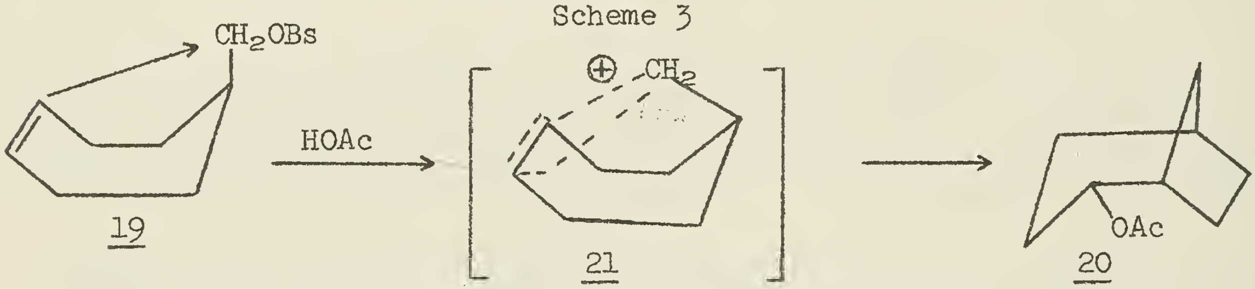
The solvolysis of endo-bicyclo[5.1.0]oct-3-yl brosylate (32) in buffered acetic acid at room temperature was complete after 48 hours. The solvolysis products from 32, after LAH reduction, can be explained by a combination of a concerted mechanism (mechanism A) and a mechanism proceeding through carbonium ion intermediates (mechanism B). The solvolysis products from 32 (Scheme 6) via the concerted mechanism (A) were 33 (58%), and 34 (18%), and via mechanism B were 35 (17%) and 36 (7%). Since no 37 was formed, an "S_N2 type" mechanism was excluded. In a control experiment, the exo isomer (37) was shown to be thermodynamically more stable than the endo isomer (34). Most of the product (76%) can be accounted for by the concerted mechanism (A) (Scheme 6).

The solvolysis of exo-bicyclo[5.1.0]oct-3-yl brosylate (38) in buffered acetic acid at 60° was complete after 24 hours. The products after LAH reduction were 33, 10%; 34, 71%; and 39, 19% (Scheme 7). The concerted mechanism (A) explains a minor portion of the product (33), and a second mechanism (C) explains the formation of 39: endo attack of the acetate ion at C-6, followed by a 1,2-hydride shift from C-6 to C-7, which is then followed by a cyclopropane ring rearrangement in a concerted manner. The formation of the major product (34) is explained by an "S_N2 type" attack by

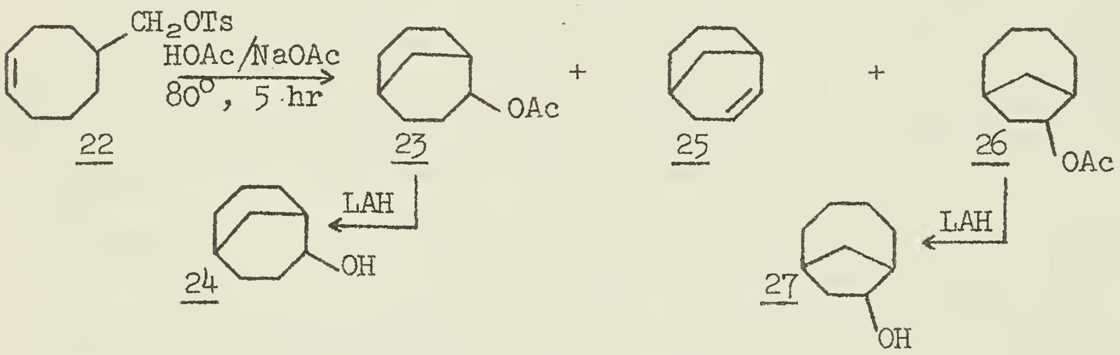
Table 2.[5,7,8] Solvolysis Products of 1 and 2

Reactant	Solvent	% Normal Products diol	 ene-ol	% Transannular Products diol	 ene-ol
1	CF_3COOH	0	0	56	43
2	CF_3COOH	0	0	0	100
1	HCOOH	13	1	53	33
2	HCOOH	24	2	36	36
1	$HOAc-OAc^-$	77	0	9	11
2	$HOAc-OAc^-$	46	21	5	23

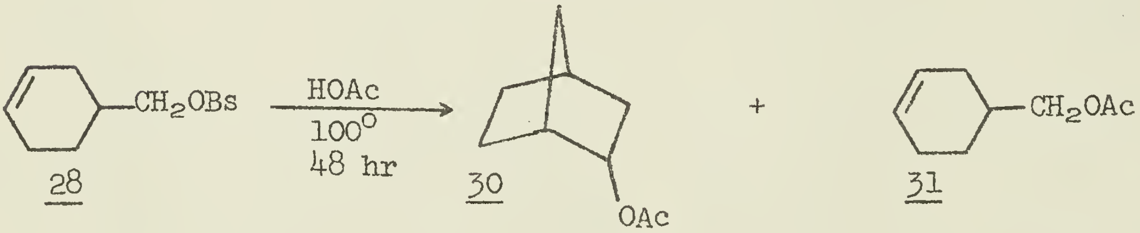
Scheme 3



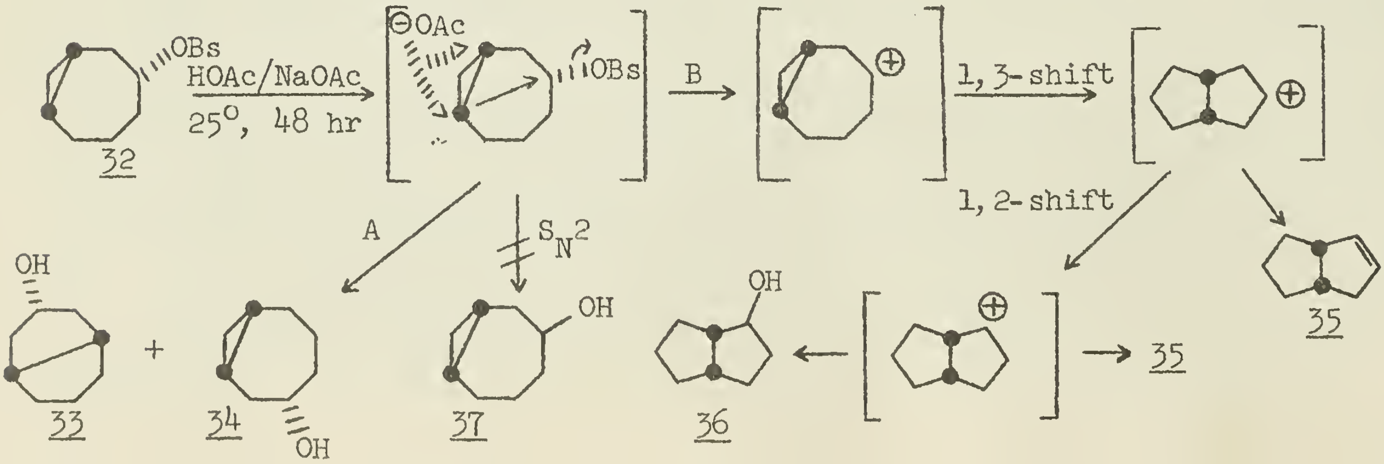
Scheme 4



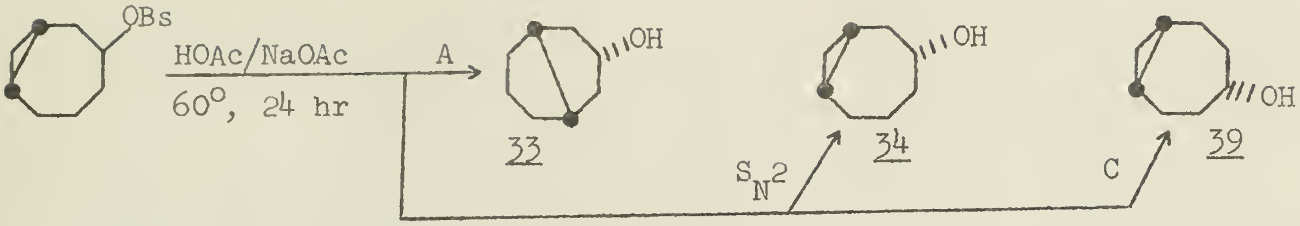
Scheme 5



Scheme 6



Scheme 7



acetate ion at C-3 of 38. However, the formation of 34 may also be explained by the concerted mechanism (A), but since in the solvolysis of 32 using the concerted mechanism (A) only 18% of the product was explained, the large amount of product formed (71%) in the solvolysis of 38 seems to indicate that an additional mechanism is also competing (the S_N2 mechanism).

The solvolysis of endo-bicyclo[5.1.0]oct-4-yl brosylate (40) in buffered acetic acid at 63° was complete after 24 hours. The products after LAH reduction (Scheme 8) were 41, 69%; 33, 0.6%; 39, 4%; and 42, 26%. The formation of 39, 41, and 42 are explained by a common carbonium ion intermediate (43): 41 by an E1 mechanism; 39 and 42 by an S_N1 mechanism. Compound 42 can also be formed by a direct displacement. The formation of 33 can be explained by mechanism (D), in which the attack by the acetate ion is followed by participation of the cyclopropane ring and then a 1,2-hydride shift (44) in a concerted manner.

The solvolysis of exo-bicyclo[5.1.0]oct-4-yl brosylate (45) in buffered acetic acid at 63° was complete after 24 hours. After a LAH reduction, the products (Scheme 9) were 41, 43%; 39, 44%; and 42, 13%. The products (39, 41, 42) are explained by the common carbonium ion intermediate (43), followed by an E1 mechanism (41) and an S_N1 mechanism (39 and 42). Compound 39 can also arise via an S_N2 mechanism. The presence of some S_N2 mechanism in the solvolysis of both 40 and 45 is shown by the amounts of 39 and 42 formed because the endo-alcohol (39) is expected from the exo-brosylate (45), and the exo-alcohol (42) is expected from the endo-brosylate (40). If the solvolysis of 40 and 45 had proceeded only through the S_N1 mechanism, the more stable exo-alcohol (42) would have predominated over the less stable endo-alcohol (39). However, in the solvolysis of the exo-brosylate (45) (Scheme 9), the endo-alcohol (39) predominates over the exo-alcohol (42).

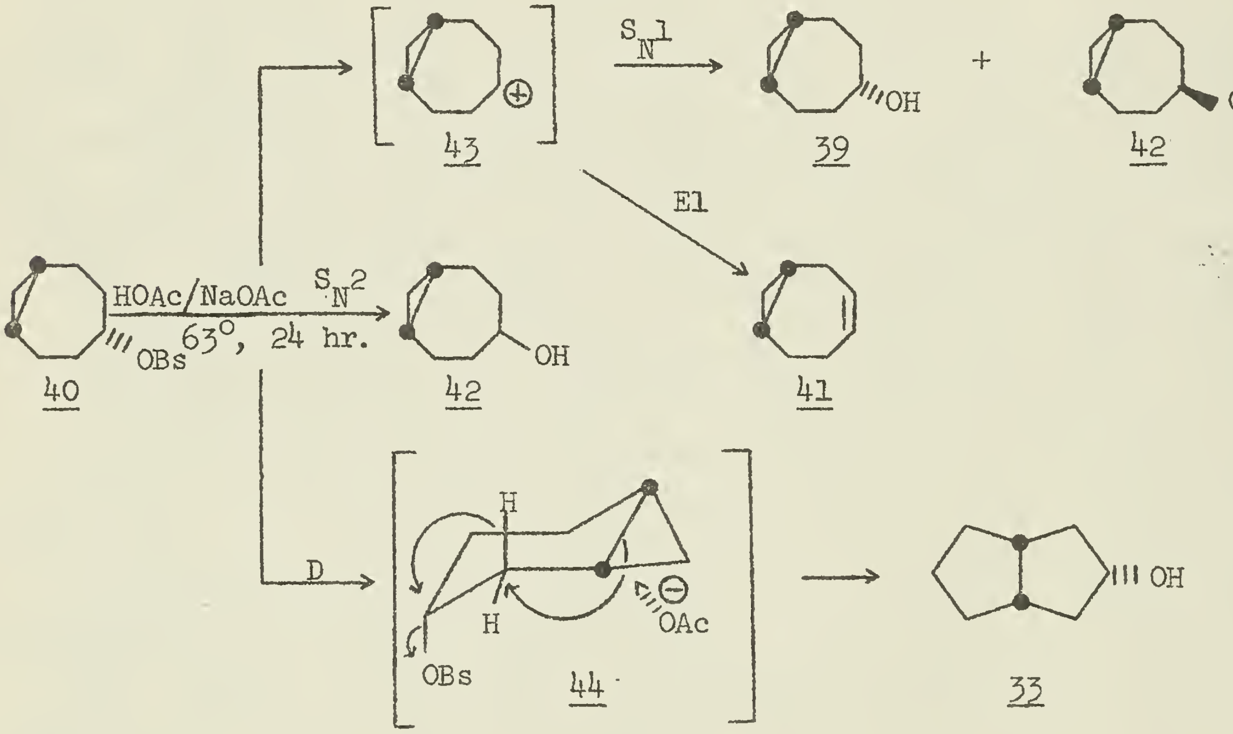
Participation of a cyclopropane ring with a developing carbonium ion which is separated by more than one carbon was recently studied.[16] The acetolysis of 46 at 25° (Scheme 10) gave only 3-homoadamantyl acetate (47). Using a similar system, the participation of the π-electrons of a double bond was also studied.[16] The acetolysis of 48 at 25° (Scheme 10) gave only 1-adamantyl acetate (49). It is well known that the amount of participation a cyclopropane ring can provide is highly dependent upon its orientation with respect to the developing carbonium ion.[17] In Table 3, the relative rate of solvolysis of three model compounds (50, 51 and 52) are compared. Since the solvolysis of 52 is slower than 50 and 51, this indicates that in general a cyclopropane ring provides better anchimeric assistance than a double bond. When comparing the relative rates (Table 4) of solvolysis of 46 and 48 with cyclohexyl tosylate (53), there is little difference in the anchimeric assistance afforded by the transannular groups. However, since the products of the solvolysis of 46 and 48 are results of the transannular reaction, both the cyclopropane ring and the π-electrons of the double bond are participating in the transannular reaction.

The acid catalyzed opening of cyclooctene oxide has been shown to involve a hydride shift. In order to understand the 1,3-versus the 1,5-hydride shift to an electron-deficient center, some substituted cyclooctanes were studied.[18-20] The solvolysis of *cis*-5-*t*-butylcyclooctyl tosylate (54) at 75° in acetic acid occurs with nearly 100% transfer of a hydride from C-5 to C-1. The solvolysis of 3-*t*-butylcyclooctyl tosylate (55) (*cis* and *trans* isomers were inseparable) in refluxing acetic acid for 16 hours yielded a mixture of products (Scheme 11).[20]

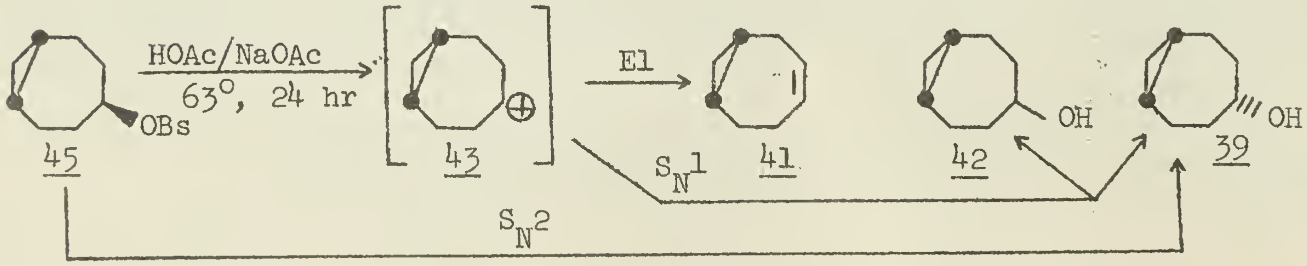
Even though the results of 55 are not as clean as the results from 54, one can conclude that 1,3-hydride shift in the solvolysis of cyclooctyl tosylates does not occur to any large extent even when a *t*-butyl group is placed at C-3 so that the carbonium ion resulting from transannular hydride migration would be tertiary rather than secondary.

A summary of the rates of solvolysis of several tosylates is given in Table 5. In comparing the simple straight chain tosylate (57) with the cyclooctyl tosylate (56), an excellent example of I strain[21,22] is seen. During the solvolysis of 56, the unfavorable torsional strain is relieved to some extent as the transition state attains some carbonium ion type geometry. The slower rate of solvolysis of the *trans*-5-*t*-butylcyclooctyl tosylate (58) as compared with 56 is thought by Allinger to be due to some small, unfavorable steric effect. Compound 54 is thought to be somewhat faster than 56 because of a slight neighboring group participation and a slight steric effect, whereas, 55 is intermediate between 56 and 54 because a slight steric effect of the *t*-butyl group is operating without any neighboring group participation.

Scheme 8



Scheme 9



Scheme 10

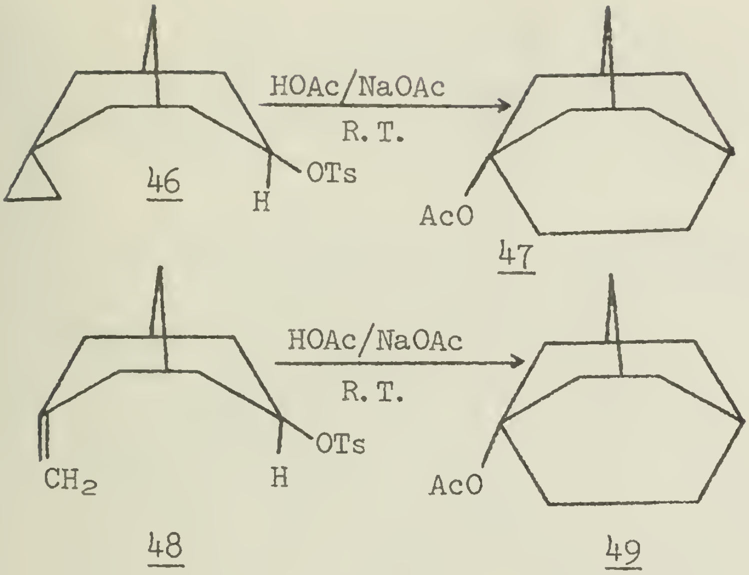
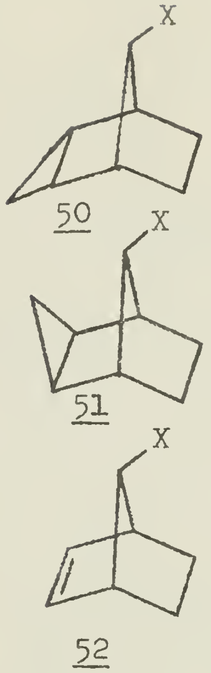


Table 3.



Relative Rate

$k_{50}/k_{51} = 10^{15}$

$k_{51}/k_{52} = 10^{3}$

Scheme 11

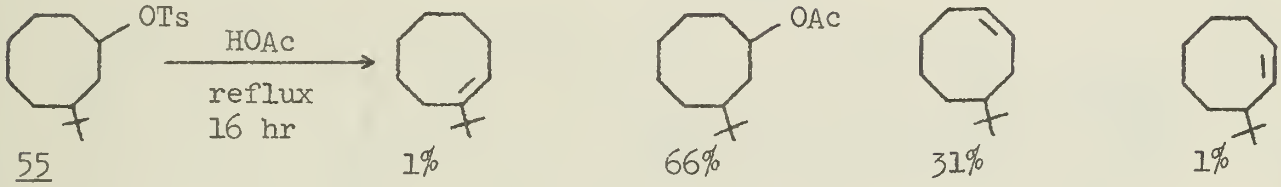


Table 4.

Relative Rate at 25°
$\frac{k_{46}}{k_{53}} = 4500$
$\frac{k_{48}}{k_{53}} = 13,500$

Table 5.

Compound	Rate Constant, sec^{-1}	Relative Rate
2-Pentyl tosylate (57)	3.2×10^{-6}	1
cis-5-t-Butylcyclooctyl tosylate (54)	9.97×10^{-4}	312
trans-5-t-Butylcyclooctyl tosylate (58)	2.92×10^{-5}	9.1
Cyclooctyl tosylate (56)	1.26×10^{-4}	39
3-t-Butylcyclooctyl tosylate (55)	5.46×10^{-4}	171

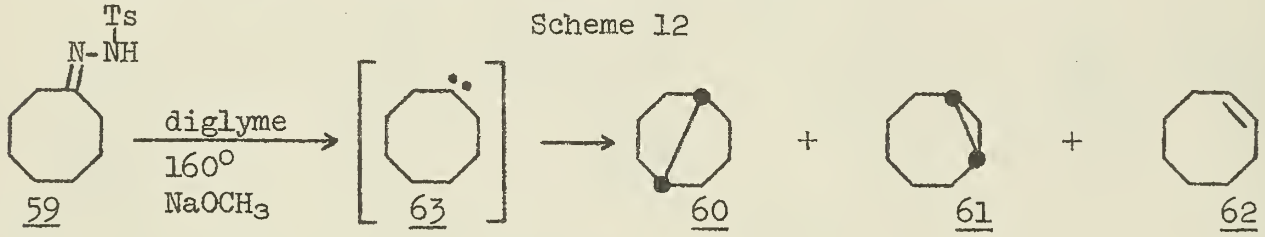
CARBENE INTERMEDIATES

The base-promoted decomposition of p-toluenesulfonylhydrazones (tosylhydrazones) in an aprotic solvent proceeds through a carbene intermediate.[26] Therefore, if the base-promoted decomposition of cyclooctanone tosylhydrazone (59) in an aprotic solvent (diglyme) yielded any transannular products, the products would be assumed to arise via a carbene intermediate. The aprotic decomposition of 59 yielded 60, 46%; 61, 9%; 62, 45% (Scheme 12). The products from 59 can be explained through the carbene intermediate 63 (Scheme 12). A 1,5-hydrogen atom shift from 63 yields 60, and a 1,3-hydrogen atom shift from 63 yields 61. The unsaturated product (62) is a result of a 1,2-hydrogen atom shift from 63. Therefore, from the decomposition of 59, 55% of the products can be explained as a result of a transannular reaction. The base-promoted decomposition of medium-ring, phenyl substituted tosylhydrazones in aprotic solvents may reveal the relative reactivity of benzylic versus nonbenzylic hydrogen in a transannular reaction. The base-promoted decomposition of 2-phenylcyclooctanone tosylhydrazone (64) in diglyme[28] (Scheme 13) yielded 65, 18%; 66, 42%; 67, 15%; 68, 4%; 69, 3%; and 70, 17%. The products from 64 arise from the intermediate 71 via a 1,3-hydrogen atom shift (69 and 70, 20%), a 1,5-hydrogen atom shift (67 and 68, 19%), and a 1,2-hydrogen atom shift (65 and 66, 60%).

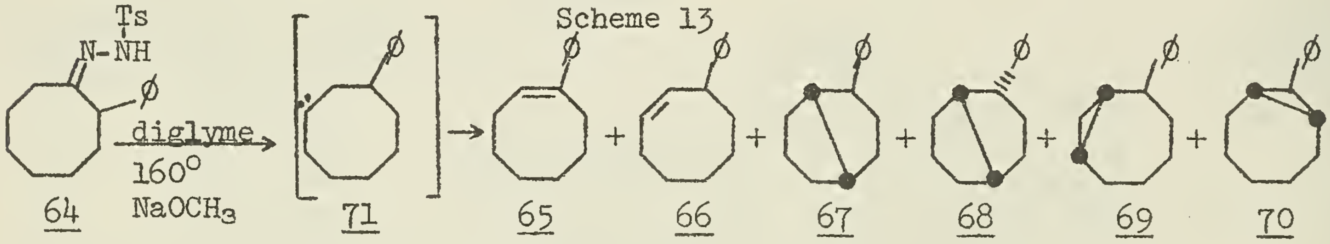
In a similar experiment, 3-phenylcyclooctanone tosylhydrazone (72) yielded (Scheme 14) 66, 40%; 73, 38%; 74, 17%; 75, 1%; 76, 2% and 2% unidentified products. The products from 72 can be explained through the carbene intermediate 77. Again, there are products as a result of a 1,3-hydrogen atom shift (75 and 76, 3%), a 1,5-hydrogen atom shift (74, 17%), and a 1,2-hydrogen atom shift (66 and 73, 78%).

There does not appear to be much selectivity between the benzylic and nonbenzylic hydrogens toward the insertion reaction. In the decomposition of 64 and 72, no significant preference was shown toward benzylic hydrogens. However, there is a larger amount of olefin formed from the phenyl-substituted compounds (64 and 72) as compared with the unsubstituted reactant (59). All of the products from the decompositions of 59, 64, and 72 can be explained by 1,2-, 1,3-, and 1,5-migrations. There were no 1,4-migrations detected in the decomposition reactions, as was also the case in the solvolysis reactions. This is thought to be a result of the preferred conformations of the eight member rings in which the 1,3 and 1,5 positions are relatively close together, and the 1,4 positions are relatively far apart. Since all of the bicyclic ring junctures are cis, the 1,3- or 1,5-axial hydrogen is believed to undergo a concerted transfer. This is shown in the products from both the carbene insertion reactions and the solvolysis reactions.

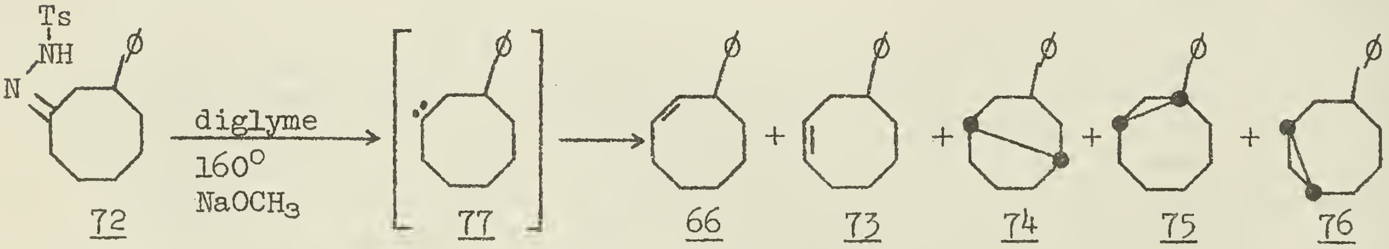
Scheme 12



Scheme 13



Scheme 14



Transannular reactions which proceed through a carbene intermediate are also known in the bicyclo[3.3.1]nonane system.[31-33] Thermal decomposition of α-diazoketones[26, 29] in ten membered rings give transannular products from carbene intermediates, as well as the peracid oxidation of triple bonds.[30]

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THE ADDITION OF SULFENYL CHLORIDES AND SULFUR DICHLORIDE TO ACETYLENES

Reported by Ronald S. Lenox   October 22, 1970

INTRODUCTION

Interest in the addition of sulfenyl chlorides and sulfur dichloride to unsaturated systems began with the Levinstein process for the manufacture of mustard gas and the subsequent investigation into the nature of the contaminants formed in the process.[1] Since then, the actions of sulfenyl halides and sulfur dichloride on olefins[2-4] and allenes have been studied extensively.[5-7] The investigation of the reactivity of acetylenes towards these reagents has been less extensive and quite fragmented, however, and it is the purpose of this seminar to examine the work done in this particular area.

STEREOCHEMISTRY OF ADDITION PRODUCTS

The first reported addition of a sulfenyl chloride to an acetylene was done in 1946[1] when 2-chloroethyl-2-chlorovinylsulfide was produced by adding 2-chloroethylsulfenyl chloride to acetylene. In 1953, it was reported that the addition of 2,4-dinitrobenzenesulfenyl chloride to acetylene, 2-butyne, 3-hexyne and diphenylacetylene gave 1:1 adducts with sharp melting points.[8] In the case of acetylene, catalysis by aluminum trichloride was required. Yields as high as 92% were observed with diphenylacetylene.

The *trans* addition of sulfenyl chlorides to olefins suggested that similar stereochemistry would apply in addition to acetylenes. Proof of the stereochemistry has come from several groups,[9-14] and two examples of this work, one based on chemical and the other on spectroscopic analysis, are illustrative. Kharasch[9] found (Fig. 1) that reaction of 2,4-dinitrobenzenesulfenyl chloride (**1**) with phenylacetylene (**2**) gave the vinyl adduct **3**. The *E* configuration was suggested by comparison with the products from an alternate route via the dichloride **6**. The major product from this route was a compound having a chlorine analysis, ir spectrum and melting point (141.5-142°) identical with the adduct formed from the reaction of **1** and **2**. The phosphorus pentachloride pathway also gave a small amount of a second compound (mp 154.5-156°) which was believed to be the *Z* isomer **7** on the basis of chlorine analysis and the ir spectrum.

Another group has prepared the series of isomers shown in Fig. 2[10] according to a modification of a procedure given by Kharasch.[9] These represent all possible vinyl adducts from the reaction of **1** with 1-phenylpropyne. When the reaction between **1** and 1-phenylpropyne was carried out, *only* isomers **8** and **9**, both resulting from *trans* addition, could be detected. The correct stereochemistry was established by nmr spectroscopy since for a given *cis-trans* pair, the methyl group *cis* to phenyl is at higher field than methyl *trans* to phenyl.[15]

In some cases[12,16,17] a small amount of *cis* addition product has been detected, but this has been shown to arise from the *trans* isomer by thermal or photochemical isomerization.[12,18-22] However, in *some* cases, it has been postulated that a direct formation of the *cis* isomer is occurring since isomerization alone does not account for the large amounts of *cis* isomer encountered.[21] A more thorough investigation of this area is needed before any definite conclusions regarding a duplicity of mechanisms can be drawn.

The addition of sulfur dichloride to acetylenes is more complex than addition of aryl sulfenyl chlorides as the reaction does not always stop with the formation of a 1:1 olefinic adduct. Addition of freshly distilled sulfur dichloride to an ethereal solution of 3-hexyne produced a colorless liquid in 95% yield.[23] The 1:2 adduct structure **12** was assigned to this compound on the basis of mass spectrum (molecular ion m/e 266), elemental analysis, nmr spectrum (which showed only two types of non-equivalent ethyl groups), and conversion of the corresponding sulfone into propionic acid by ozonolysis. Initially it was the author's expectation that the addition of sulfur dichloride to an acetylene would provide a facile path to thiiranes as shown in Fig. 3.[23] It was felt that ring closure would result from internal attack of the sulfenyl chloride upon the adjacent double bond. However, no thiirane could be detected from this reaction and dilution and temperature had no effect on either the nature or yield of products.

The addition of sulfur dichloride to diphenylacetylene in ether follows a different course. The isolated product was a bright yellow solid which lost hydrogen chloride upon standing to give 3-chloro-2-phenylbenzo[b]thiophene (13).[23] The intermediate product has been proposed to be the 1:1 adduct 14 resulting from *trans* addition although a thermal rearrangement of a thiirane could also lead to the same product.[24,25] Evidence for this has been obtained by preparing the derivatives shown in Fig. 4. It can be seen that the reaction of 14 with diphenylacetylene gives the 1:2 adduct which is analogous to 12. The difference between the reactivity of alkyl and aryl acetylenes toward sulfur dichloride is mainly the stability and reactivity of the 1:1 adduct as represented by structure 14.

One example of possible synthetic utility of the combination of sulfur dichloride with acetylenes is shown by its reaction with diphenylbutadiyne which gives 3,4-dichloro-2,5-diphenylthiophene (15), although in low yield.[23]

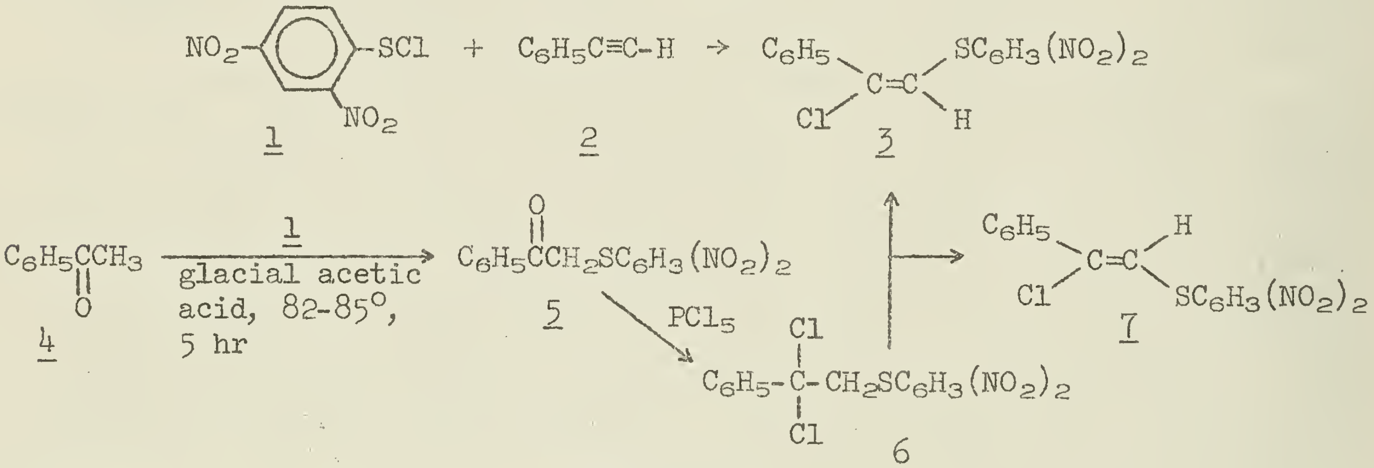


Fig. 1

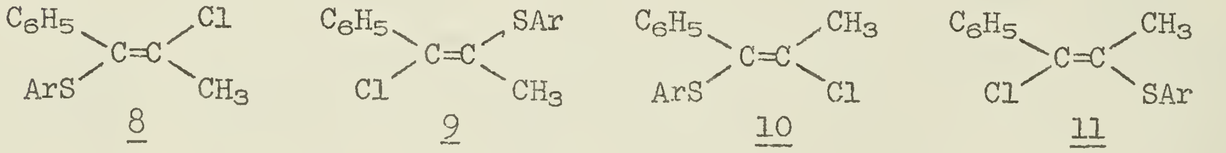
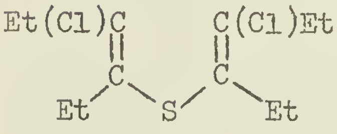


Fig. 2



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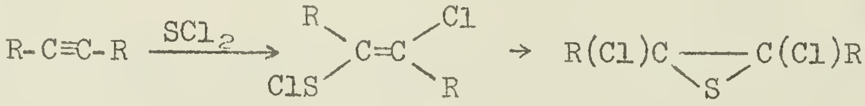
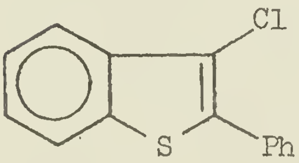


Fig. 3



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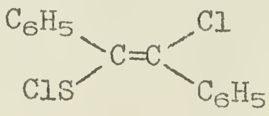

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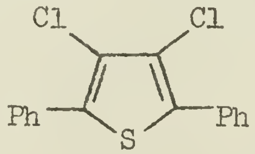

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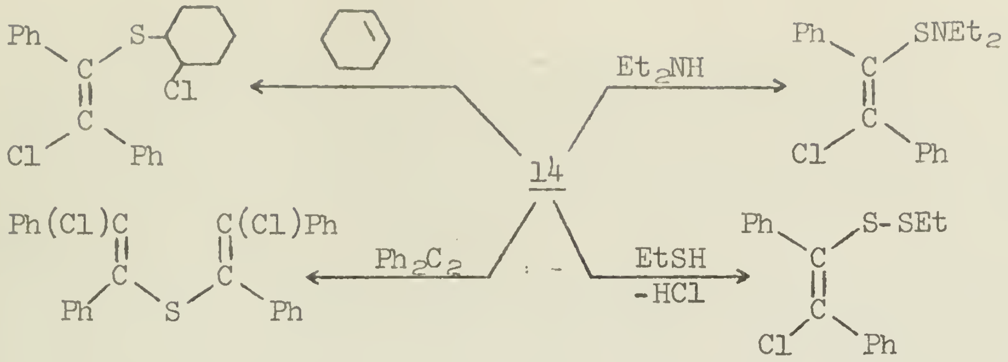


Fig. 4

ORIENTATION OF ADDITION

Perhaps the most interesting aspect of the additions to alkynes is the ratio of anti-Markovnikov (AM) product to Markovnikov (M) product which is observed whenever an unsymmetrical acetylene is employed. In olefins, the product is the generally expected M isomer[17] with chlorine attached to the carbon which could form the most stable carbonium ion and thus product orientation can be quite easily predicted. With acetylenes, a certain amount of controversy existed over orientation of addition until it was realized that differing results concerning orientation were in fact opposite cases which could be explained by the same mechanistic process.[26] More particularly, the ratio of M to AM products depends on several factors such as the nature of the solvent employed, the substitution encountered on the acetylene and the type of sulfenyl chloride being utilized.

SOLVENT EFFECTS

The influence of the solvent environment upon the M/AM ratio is quite pronounced. For instance, the data shown in Table 1 were obtained by examining the products of the reaction of *p*-nitrobenzenesulfenyl chloride with phenylacetylene.[26] Similar data have been obtained on solvent effects using 1 and 1-phenylpropyne.[10] The product distributions shown in Table 2 resulted from analysis of the products.

It is readily observed that the use of acetic acid gives a higher proportion of the M product in both cases. The effect of solvent cannot be related to dielectric constant of the medium[16] since acetic acid and ethyl acetate have similar dielectric constants (6.15 and 6.09 at 20°, respectively)[27] but very different effects on the orientation of addition. Chloroform and acetonitrile have greatly different dielectric constants (4.8 and 37.5 at 20°, respectively)[27] but very similar effects on addition.[16] Clearly, some other property of the solvent must be responsible.

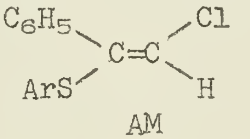
If the acidity of the solvents is examined, however, a good correlation can be observed. To demonstrate the acid dependency of orientation, the addition of *p*-nitrobenzenesulfenyl chloride to phenyl acetylene was studied using ethyl acetate as a solvent.[21] Varying amounts of acid were then added and the product ratios determined. The amount and type of acid added and the product ratios are shown in Table 3. It is evident that there is a direct correlation between the amount of M product and the acidity of the reaction mixture. It has also been suggested that acidity and the specific ability to solvate the chloride ion are important.[21] (See section on Mechanistic Proposals.)

Solvent effects with sulfur dichloride reactions are not well investigated and hence not well understood. As mentioned previously, the addition of sulfur dichloride to diphenylacetylene in ether gave 13 via the 1:1 adduct. However, if the reaction was run in methylene chloride, hexane or acetonitrile only the 1:2 adduct (16) could be detected.[23] Here, ether must play a special role, presumably by solvating the intermediate sulfenyl chloride 14 and reducing its reactivity.

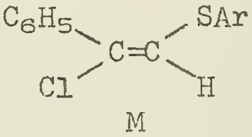
Examination of the reaction of sulfur dichloride with unsymmetrical acetylenes shows only minor solvent dependency. To see if both M and AM addition could be observed, both phenylacetylene and 1-phenylpropyne were studied.[23] Reaction of two equivalents of phenylacetylene with sulfur dichloride in ether or methylene chloride provided the divinyl sulfide 17 while equimolar amounts yielded only the vinylsulfenyl chloride 17a, both of which are AM products. If the M product had formed, the resulting sulfenyl halide would be expected to form 3-chlorobenzo[b]thiophene. Even by carrying out the reaction in acetic acid, only 16% of the product, as determined by nmr, was the desired thiophene. This suggests that steric factors in the reaction may play an important role,[23] although the addition of sulfenyl chlorides to phenylacetylene seems to give mainly the M product when carried out in acetic acid.

Table 1. Solvent Effects with Phenylacetylene

Solvent	AM(%)	M(%)
Ethyl Acetate	85	15
Chloroform	65	35
Acetic Acid	20	80



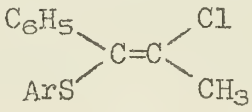
AM



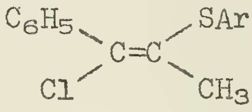
M

Table 2. Solvent Effects with 1-Phenylpropyne.

Solvent	AM(%)	M(%)
Benzene	17	83
Ethyl Acetate	13	87
Chloroform	6	94
Acetic Acid	0	100



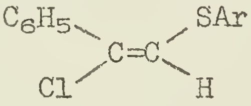
AM



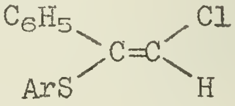
M

Table 3. Effect of Acid on Orientation

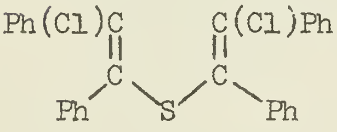
Acid	Amount (g/100 ml solvent)	AM(%)	M(%)
None	None	85	15
CF_3COOH	3.6	69	31
	5.8	55	45
	11.3	46	54
HCl	5.0	43	57



M



AM



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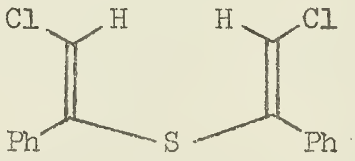

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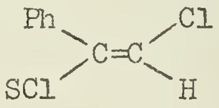


17a

SUBSTITUENT EFFECTS

Solvent is not the only influencing parameter as has been previously noted. Work with substituted tolanes[28] has shown that there is a definite relationship between the orientation of addition and the substituent on the aromatic group of the tolane. For example, Table 4 shows the products obtained from the reaction of p-tolylsulfenyl chloride and variously substituted tolanes.[28] The solvent used in all cases is ethyl acetate. When aromatic substitution is such that an intermediate vinyl carbonium ion would be well stabilized, then the product formed will have the chlorine bound to the carbon which carried the positive charge. In the case of p-OCH_3, only the M isomer is formed, thus indicating an effect of the strong electron donating tendency of the methoxyl group.

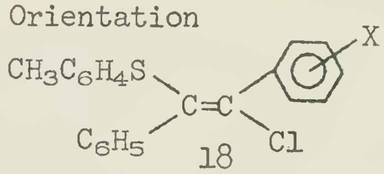
Quite satisfactory Hammett plots can be constructed when sigma+ values are used. Figures 5 and 6 give such plots for two solvents, chloroform and ethyl acetate respectively, when p-tolylsulfenyl chloride was added to substituted tolanes.[28] Of special interest is the relatively high negative value of rho in both cases. This, together with the use of sigma+, indicates a highly polar transition state with the acetylenic component having a nucleophilic role.

More recent work also indicates the relationship between the substituents on the acetylenic component and orientation.[16] By adding substituted sulfenyl chlorides to both 1-butyne and phenylacetylene in different solvents as shown in Fig. 7, the data shown in Table 5 were collected. In the case of phenylacetylene, the percentate of the M isomer is greater in every instance, indicating the substantial difference between aryl and alkyl substituents on the acetylene. This again points to the polar nature of the reaction and the effect of charge stabilizing substituents on the alkyne. Other examples of such effects are known[11] and support the previous data. Substitution on the electrophilic sulfenyl chloride is also a determining factor although the magnitude of such influence is lower than for substitution in alkynes.[16] Rates of addition of substituted phenylsulfenyl chlorides to tolane in chloroform at 25° have been studied.[26] The data presented in Table 6 cannot be fit to a satisfactory Hammett plot although a direct relationship between rate and electron donating potential exists. A private communication to Calo'[26] has indicated that the addition of 2-nitro-4-X-benzenesulfenyl chloride to cyclohexene gives a satisfactory Hammett plot when sigma+ values are used. Unfortunately, no data accompany this report.

Nevertheless, the directive influence of the chlorides is somewhat increased by electron withdrawing substituents, particularly on aryl sulfenyl chlorides. This effect appears to be greater in less acidic solvents. The data presented in Table 7 show both of these phenomena where substituted (X) benzenesulfenyl chlorides were added to phenylacetylene.[28] It has been suggested that the o-NO_2 group should be considered a special case[16] which is discussed in greater detail in the section entitled Kinetics. If this is so, then the nature of the sulfenyl chloride affects the orientation only in a minor way and in limiting cases.

Table 4. Effect of Tolane Substitution on Orientation

Tolane	18(%)	19(%)
X = H	one compound	
X = p-OCH_3	100	0
X = m-Cl	20	80
X = p-Cl	60	40



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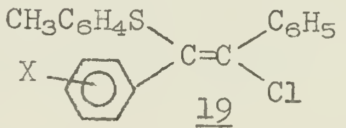

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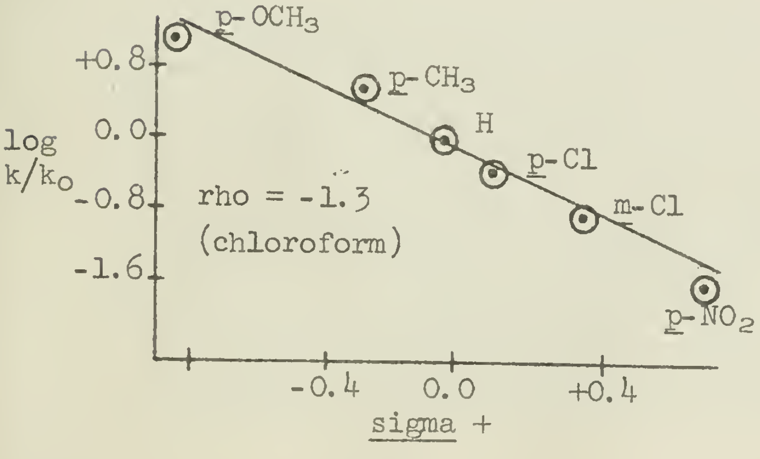


Fig. 5

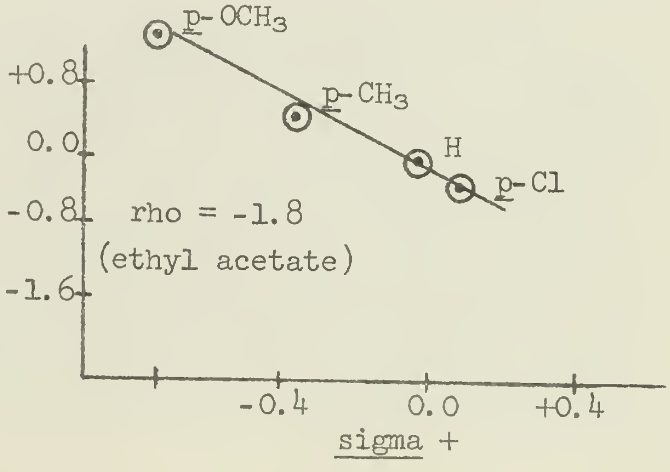


Fig. 6

Addition of p-Tolylsulfenyl Chloride to Substituted Tolanes

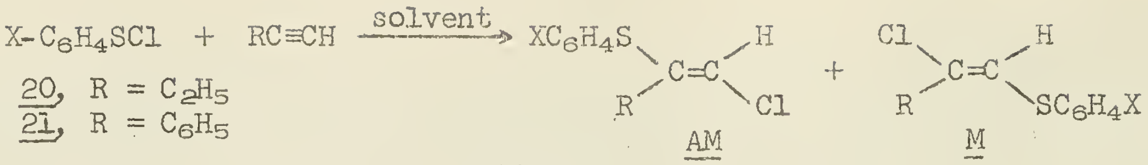


Fig. 7

Table 5. Effect of Sulfenyl Chloride Substitution on Orientation

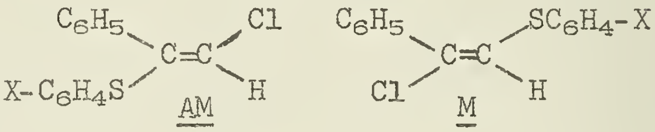
X	Solvent	20 AM(%)	20 M(%)	21 AM(%)	21 M(%)
p-NO_2	Ethyl Acetate	100	0	85	15
	Acetic Acid	100	0	20	80
o-NO_2	Ethyl Acetate	80	20	57	43
	Chloroform	67	33	45	55
	Acetic Acid	58	42	11	89

Table 6. Rates of Addition for Substituted Aryl Sulfenyl Chlorides

Rate	X = p-OCH_3	p-CH_3	H	p-Cl	p-NO_2
k x 10^3 $sec^{-1}mol^{-1}lit$	170	190	159	77	6.9

Table 7. Solvent Effects on Orientation of Addition of Substituted Benzenesulfenyl Chlorides

X	Solvent	AM(%)	M(%)
p-CH_3	Ethyl Acetate	100	0
p-NO_2		85	15
o-NO_2		57	43
p-CH_3	Acetic Acid	29	71
p-NO_2		20	80
o-NO_2		11	89



KINETICS

The rates of addition of 1 to both phenylacetylene and 3-hexyne have been determined.[9] The reactions were carried out in anhydrous acetic acid and followed by measuring the rate of disappearance of the chloride.[29] With phenylacetylene, the reaction was quite slow at both 35° and 45°, although satisfactory measurements were obtained at 45° and 55°. The reaction of 3-hexyne was much faster and could be measured at 35° and 45°. Both showed simple second order kinetics, first order in each reagent, and no indications of any deviation could be found. The data resulting from this work appear in Table 8.

Rate studies have also been done for the addition of p-tolylsulfenyl chloride to tolane and 1-hexyne.[28] Results of this work are shown in Table 9. Of interest is the dependency of the rate upon the type of solvent. The results of these studies parallel previous findings on the additions to alkyl acetylenes.[30]

When compared with olefins, acetylenes have been found to react slower in most cases.[9,30,32] For example, the addition of 1 to phenylacetylene is 1/100 as fast as addition to styrene.[9] It has been proposed that this may be caused because the electrons in the π bonds of the alkyne are more tightly bound than those of the corresponding alkene. It is also known that stilbene is 250 times more reactive toward bromine than is diphenylacetylene.[33] Strikingly different results are found when sulfur dichloride is employed.

It is found that a competition experiment using *trans*-stilbene and diphenylacetylene gave almost exclusively products derived from the alkyne.[23] Similar results were found when phenylacetylene was used.

Another interesting competition between alken and alkyne centers has been done using vinylacetylene and methylsulfenyl chloride.[32] When these were caused to react at -20° in methylene chloride, 8% of the product resulted from attack at the acetylenic center. At higher temperatures, attack occurred only at the olefinic portion of the molecule. It is also known that sulfur dichloride and sulfenyl chlorides prefer to attack acetylenes rather than the olefinic products derived from them. This is, however, not at all surprising as the vinyl products have in all cases electronegative substituents which decrease the availability of the π electrons.[23]

As has been mentioned earlier in this paper, rates are also affected by the substitution encountered on sulfenyl chlorides.[26] With arylsulfenyl chlorides, *o*-NO_2 groups seem to limit the effects of solvent and the acetylenic substrate.[15] Other *ortho* substituents such as methyl and chlorine have only minor effects. The *o*-NO_2 and 2,4-dinitrophenyl derivatives react 2000-3000 times more slowly than other benzenesulfenyl chlorides.[16] It is believed that this may be the result of the strong interaction between the sulfur atom and the nitro group which has been shown to exist in the solid state by X-ray diffraction studies of the methyl ester of *o*-nitrobenzenesulfenic acid.[34]

Table 8. Rates of Addition of 2,4-Dinitrobenzenesulfenyl Chloride

Reagent	Temp °C	Rate $(mol/l)^{-1}sec^{-1}$	Ea (kcal/mol)	ΔS (e.u.)
Phenylacetylene	45.00 ± .02	2.67×10^{-5}	24.3 ± 1.3	- 3.3 ± 4.1
	55.00 ± .02	8.61×10^{-5}		
3-Hexyne	35.00 ± .02	1.29×10^{-3}	16.1 ± .07	-19.7 ± 2.2
	45.00 ± .02	2.94×10^{-3}		

Table 9. Solvent Effects on Reaction Rates

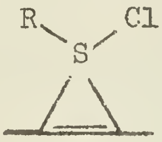
Reagent	Solvent	T(°C)	$k \times 10^3$ $sec^{-1}mol^{-1}l$	Ea kcal/mol	ΔS (e.u.)
Tolane	Chloroform	0	116		
		15	154		
		25	190	3.1	-53
	Ethyl Acetate	25	0.093		
1-Hexyne	Chloroform	25	199	4.8	-47
	Ethyl Acetate	25	9.07	7.4	-45

MECHANISTIC PROPOSALS

Mechanisms proposed for the addition involve an electrophilic role for the chloride with the acetylene acting as the nucleophile.[16, 22, 23] Two groups[22, 23] have proposed an initial covalent complex which involves tetravalent sulfur (22). From this, either a tight (23) or loose (24) ion pair may be formed, depending on the nature of the solvent. In a more acidic solvent, the loose ion pair would be preferred. Markovnikov addition would result if the substitution on the acetylene or the acidity of the solvent were such as to allow a buildup of positive charge on a vinyl carbon atom. Solvation of the chloride ion by an acidic medium would allow the two-step polar addition necessary for M addition.[21]

AM addition is not as well understood. One worker has postulated that the tight ion pair may collapse by an unknown pathway to give the observed products.[16, 22] More recently, it has been suggested that steric crowding in the transition state[23] forces nucleophilic attack at the less hindered center, thus giving the AM product.

The polar nature of the transition state is confirmed by an interesting rearrangement. Triphenylazulene (25) has been prepared in 25% yield based on the acetylene in the reaction of 1 with diphenylacetylene in ethylene chloride at 0° using a 1:2:1 ratio of the chloride, acetylene and aluminum trichloride, respectively.[35] The proposed polar mechanism is shown in Fig. 8.



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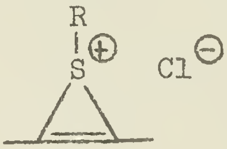

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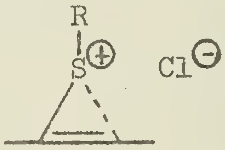

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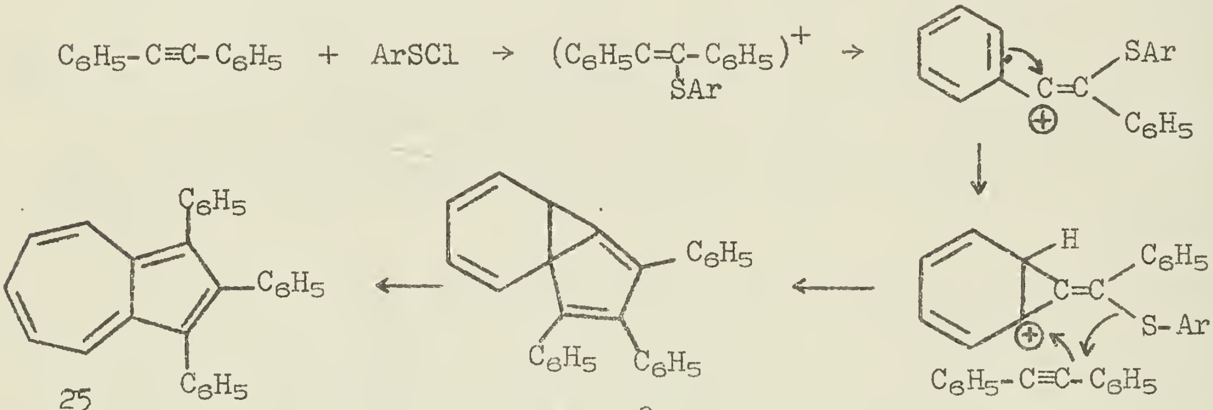

Fig. 8

CONCLUSION

Although most aspects of the additions to acetylenes have been investigated, there are still areas which need further research. The high amounts of cis products obtained in some cases, the seemingly odd kinetic behavior of sulfur dichloride with stilbene and diphenylacetylene and the behavior of o-NO_2 arylsulfenyl chlorides as well as the importance of steric factors in the transition state are all areas which are not sufficiently understood.

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REDUCTION-ALKYLATION

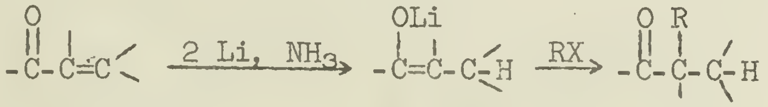
Reported by Roger L. Sowerby October 26, 1970

Reduction-alkylation is one of several methods that have been developed to circumvent the problems of over-alkylation[1] and alkylation at the wrong position[2] which often accompany normal alkylation.[2,3] In all alkylation reactions the most important step is the formation of a specific enolate anion. In the titled procedure this is done by a dissolving metal reduction of an easily reducible group α to a carbonyl moiety. The most common procedure is to add an α,β-unsaturated ketone to a lithium-liquid ammonia solution to form the enolate, and then add the appropriate alkylating agent (Scheme 1).[2,4] Hexamethylphosphoramide has also been used as a solvent,[5] and other metals (Na, K, Ca, Ba)[2,6] as well as other reducible groups (OAc, OH, Br)[6] have been used. The addition of a proton donor (*t*-BuOH, Ph_3COH, H_2O) along with the ketone has been found to eliminate most of the unreacted starting material which is often found using the above procedure. The enolate intermediate can also be carboxylated by addition of carbon dioxide[2] or cyanogen chloride[7] after first removing the ammonia.

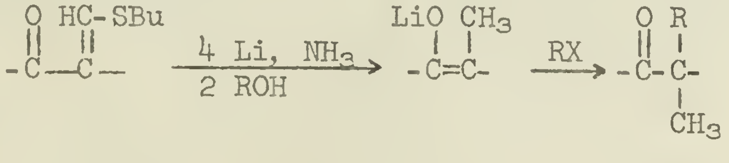
The use of the lithium enolate is very important in that it has been found that, once formed, it will not equilibrate in aprotic nonionizing solvents and that these enolates alkylate faster than they equilibrate with already formed ketone.[8] Neither of these statements hold true for the enolates of sodium or potassium.[2] The stereochemistry of the products can often be predicted from the expected geometry of the enolate intermediate, since it has been found that the transition states of these reactions apparently closely resemble the geometry of the enolate.[9]

Reduction-alkylation has been used in the synthesis of diterpenes and steroids, and it has been used extensively in the preparation of steroid analogs. Spencer has formed 2 from enone 1, and used this compound as the key intermediate in the synthesis of methyl vinhaticoate,[10] podocarpic acid,[11] and methyl deisopropyldehydroabietic acid.[12] Afonso formed 3 from testosterone acetate, which he subsequently converted into (-)sandaracopimaric acid.[13] Formation of 5 from 4 was used by Daum and Coworkers en route to the preparation of analogs of cassaine.[14] Stork and McMurry converted enone 6 into 7 by reduction-alkylation in their synthesis of *dl* progesterone,[15] and Birch and Subba Rao used this method in their synthesis of equilenin and isoequilenin.[16] There are many examples of the use of reduction-alkylation in the formation of 17-alkylprogesterones from various steroid precursors.[6,17] Also some 17-alkylcorticoid analogs have been prepared by this method. Alkylation at C-4 has been done with 17-methyltestosterone[19] and Δ^4-cholesten-3-one.[20]

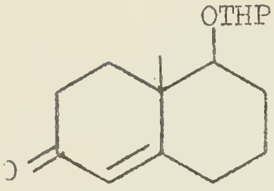
Recently work has begun on methods for the simultaneous addition of *gem*-dialkyl groups using the reduction-alkylation method. In this procedure the first step is the formation of the methylene sulfide derivative of the ketone. This is then reduced to an enolate and alkylated as shown in Scheme 2. This method has been applied to the formation of various 2-methyl-2-alkylcyclohexanones and 2,2-dimethyl-1-decalone.[21] Work is presently in progress using other cyclic and acyclic ketones as precursors to the methylene sulfide to show further utility for this reaction.



Scheme 1



Scheme 2



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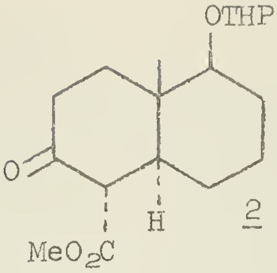

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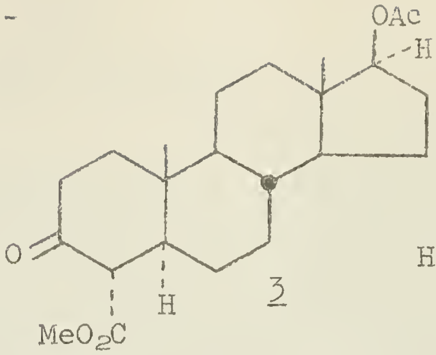

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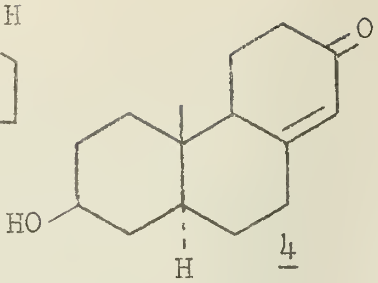

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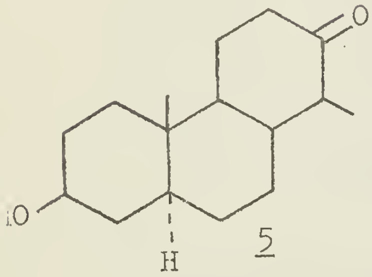

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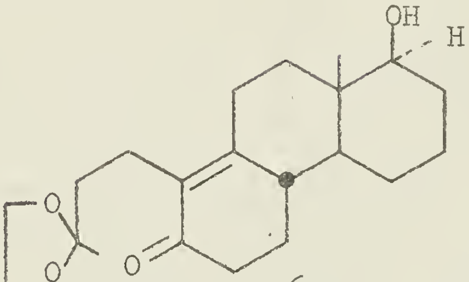

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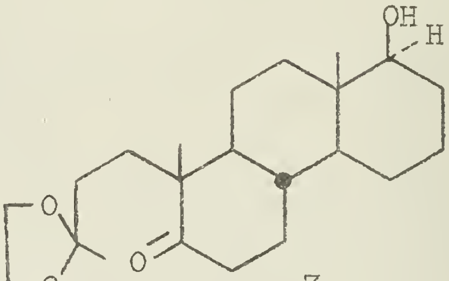

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RECENT STUDIES ON THE PRIMARY PROCESSES IN THE BIOSYNTHESIS OF STEROIDS AND TRITERPENES

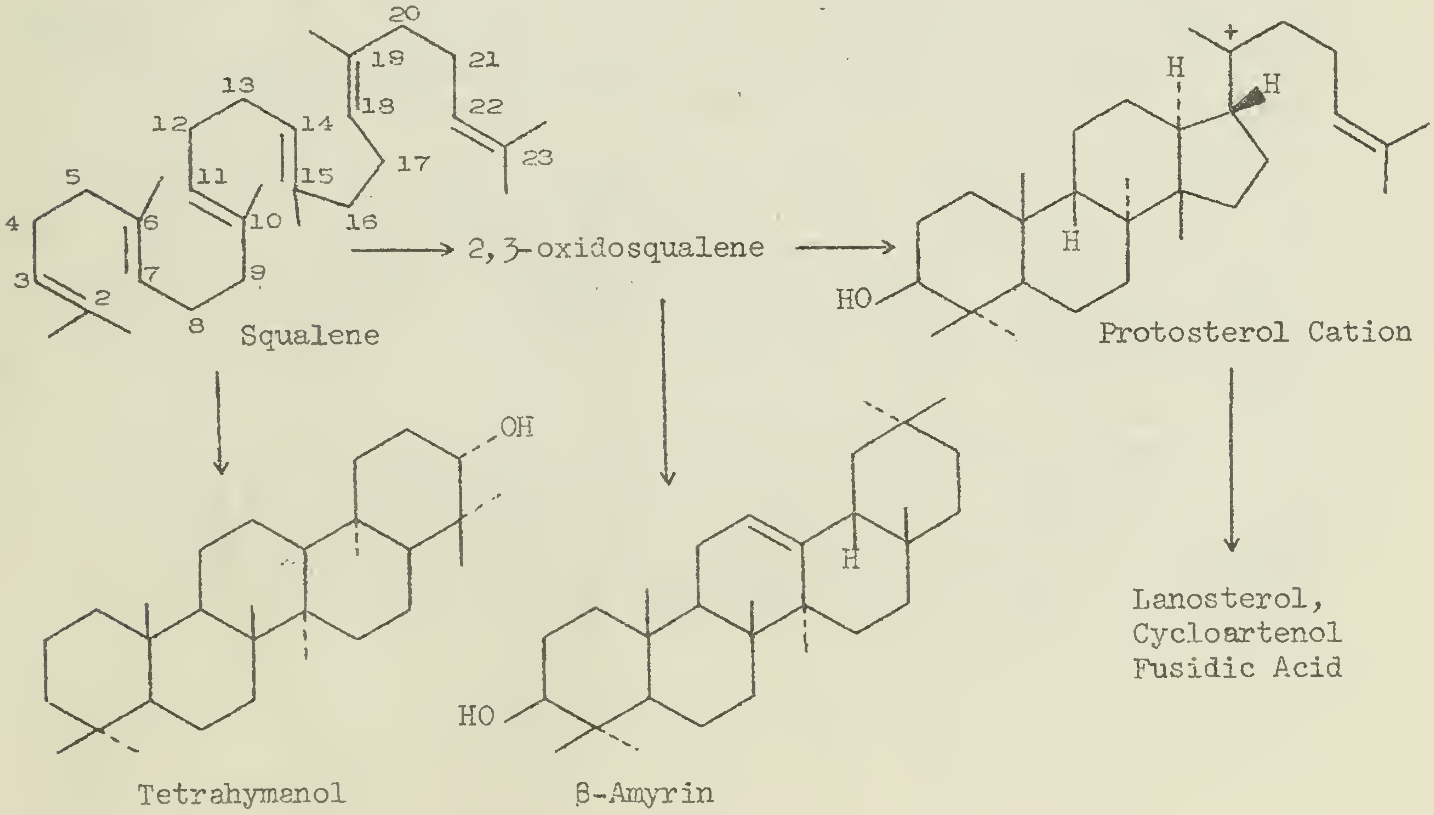
Reported by Sung Kee Chung October 29, 1970

A major aspect of the investigations of the biosynthesis of steroids and triterpenes has been the mechanistic elucidation of the conversion of squalene into lanosterol. By theoretical reasoning, squalene has been visualized as a common biological precursor not only of lanosterol and related compounds, but also of the various pentacyclic triterpenes. The biogenesis of the different cyclic triterpenes was rationalized in terms of several alternative conformations of squalene and various carbonium rearrangements.[1]

A great advance on the experimental side was the establishment of 2,3-oxidosqualene as a key intermediate in the oxidative cyclization of squalene.[2,3] Subsequent studies of cyclization using an enzymic inhibitor[4] and various unnatural epoxides[5-7] have revealed a detailed substrate specificity of 2,3-oxidosqualene-sterol cyclase. Also, the separation of the cyclization from the subsequent rearrangements[8] and the comparative study on the enzymic and nonenzymic reactivity of the substrate[2,9] gave some idea as to the stability of the protosterol cation and on the driving force of the rearrangements. By these studies and the isolation of natural prostadiene, the biogenesis of fusidic acid and related compounds could be explained.[10] The hydrogen migrations occurring during the conversion of squalene to lanosterol has been shown to be two 1,2-hydrogen shifts instead of a single 1,3-shift.[11]

Biosynthetic studies employing new enzyme preparations from pea seedlings and bean leaves for β-amyrin[12] and cycloartenol,[13] respectively, have shown very interesting results.

In contrast, cell-free extracts of yeast were found to convert lanostadiene into lanosterol, indicating that the oxidation can occur after the cyclization.[14] The concept of non-oxidative cyclization of squalene, which was originally introduced to explain the biogenesis of several 3-deoxytriterpenes,[1d] is now supported by the biosynthetic studies of tetrahymanol.[15]



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THE ASYMMETRIC SYNTHESIS OF α-AMINO ACIDS

Reported by Laurence G. Dammann November 2, 1970

INTRODUCTION

The nonenzymatic asymmetric synthesis of α-amino acids has long been a challenge to the organic chemist. The asymmetric syntheses of α-amino acids which have been reported may be divided into several groups depending on the method of preparation. Several of the earlier methods have been mentioned in a review on asymmetric reductions by Morrison.[1]

DISCUSSION

The most rational approach to the asymmetric synthesis of an α-amino acid would be through the catalytic reduction of a Schiff base derived from an α-keto acid and a chiral directing amine, since, in a broad sense it resembles the enzyme-pyridoxal phosphate catalyzed transamination reactions.[2] Hiskey and Northrop's work[3] using this method is outlined (eq. 1). The optical purity was usually high. The reactions were extended to prepare several dipeptides (optical yields ca. 50%).[4] Kanai and Mitsui,[5] who employed this procedure to prepare optically active phenylglycine using a variety of hydrogenation catalysts, proposed a steric course for the asymmetric synthesis. Harada and Matsumoto[6,7] also ran many similar "Hiskey-type" reactions to clarify the steric courses of the preparations. They also extended the method in preparing optically active α-amino acids by catalytic hydrogenation of Schiff bases and oximes of (-)-menthyl α-keto esters, followed by hydrolysis. Several α-amino acids have been prepared through the use of optically active sodium α-phenylglycinate as the chiral directing amine (optical purities 40-60%).[8,9] The mono methyl ester of aspartic acid (2) has recently been synthesized (optical purity 98%) through hydrogenolysis of a cyclic intermediate (1).[10]

The Strecker synthesis has been used to prepare alanine (optical purity ca. 90%) starting with acetaldehyde, hydrogen cyanide, and optically active α-methylbenzylamine.[11,12]

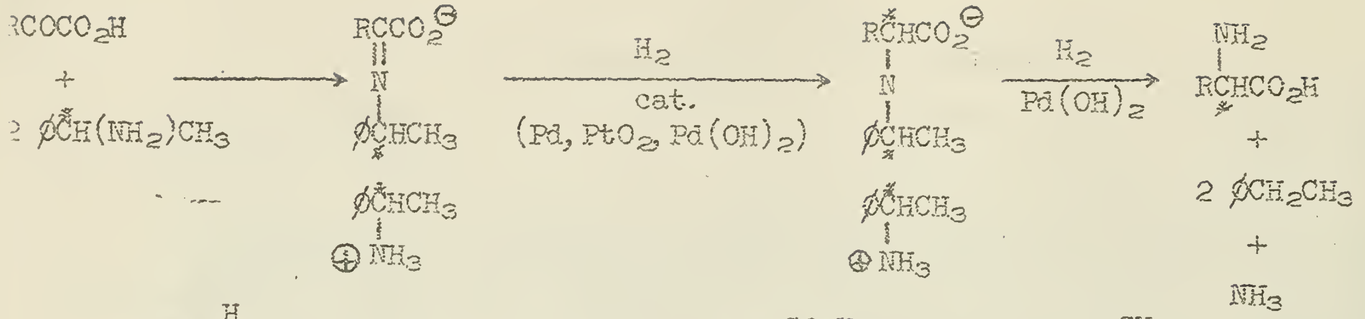
Optically active aspartic acid has been synthesized by amination of derivatives of fumaric and maleic acids with optically active α-methylbenzylamine (optical purities 5-15%).[13] It has also been synthesized from maleic acid by a similar method (88% optical purity).[14]

The reduction of β-substituted-α-acylaminoacrylyl units attached to chiral directing centers such as proline,[15] isovaline,[16] L-α-methylbenzylamine,[17] (-)-borneol,[18,19] (-)-menthol,[18-20] and α-methylphenylalanine[21] has yielded optically active α-amino acids after hydrolysis.

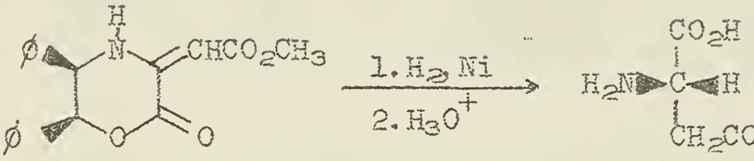
Asymmetric catalysts such as palladium on a silk support have been used to obtain optically active α-amino acids, but optical purities were low.[22,23] A special case of the utilization of metal complexation is illustrated in the synthesis of optically active threonine (ca. 8% optical yield) by hydroxyethyllation of 1-glycino-bis(ethylenediamine)cobalt (III) iodide with acetaldehyde under basic conditions.[24]

Hydrogenation, then cleavage of acylhydrazones of the type 3 are reported to give optically active α-amino acids; however, the asymmetric yields were low.[25]

Perhaps the best method described has been the one recently developed by Corey and his co-workers.[26,27] The chiral reagents used were the 1-amino-2-hydroxymethylindolines (4,5) and the 1-amino-2-(1-hydroxyethyl)-indolines (6,7). Several α-amino acids were prepared from their corresponding α-keto esters with optical purities as high as 99%, and essentially 100%, by interposing a recrystallization in the scheme. The principle advantage to this method is that the chiral reagent is not sacrificed, and is easily regenerated.



eq. 1



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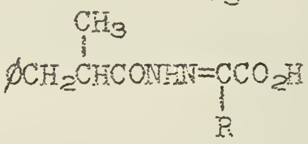

$\phi CH_2CH(CH_3)CONHN{=}C(R)CO_2H$

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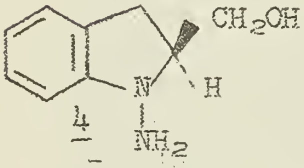

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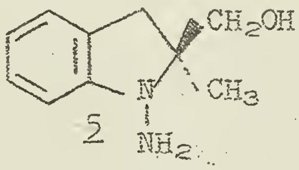

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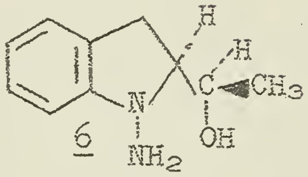

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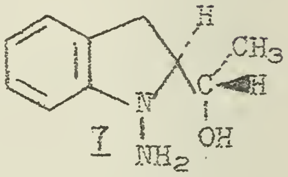

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CHEMICAL IONIZATION MASS SPECTROMETRY

Reported by Sharon Truitt November 5, 1970

Chemical ionization mass spectrometry (CIMS) is a rapidly developing technique for obtaining the molecular weight and determining the identity of certain functional groups of organic compounds. A description of the method of obtaining CI spectra was included in reviews[1,2] of CIMS applied to simple organic compounds. Present discussion will be limited to the use of CIMS with more complex molecules, photodimers of cyclic α,β-unsaturated ketones,[3] amino acids,[4] and alkaloids,[5,6] and in the elucidation of the structure of the antibiotic botryodiplodin.[7]

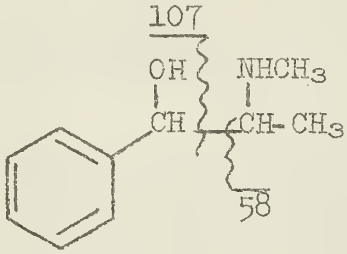
Although electron impact mass spectrometry (EIMS) has made tremendous contributions in the identification of organic compounds, its frequent failure to yield stable molecular ions (M^+) for complex organic molecules has been an unfortunate limitation. Since CIMS produces ions with much lower energy than EIMS (20 eV vs. 70 eV)[5] CI usually produces a more stable "quasimolecular ion," QM^+, at m/e $(M + 1)^+$ of significant relative abundance. Thus, CIMS has been shown to be especially useful in determining the molecular weight of molecules. Correspondingly, there are generally fewer low-mass peaks to help in structure determination. As a result CI and EI spectra frequently complement each other.

CIMS has been shown to help in differentiating between isomeric structures.[8] The relative intensities of the QM^+ and $(M/2 + 1)^+$ ions distinguish between the head-to-head and head-to-tail diketones formed by the photodimerization of cyclic α,β-unsaturated ketones.

Use of CIMS for peptide sequencing is being investigated.[5,9] To this end, the results of analyses of the CI spectra of 21 amino acids show that the identity of an amino acid can be indicated in this way.[4] Unless cyclization with loss of H_2O or NH_3 is facile, the QM^+ ion is among the more intense of the CI spectrum. Loss of $COOH_2$ from the QM^+ ion is virtually the extent of fragmentation for simple aliphatic amino acids. The mechanism for formation of $(QM\text{-}COOH_2)^+$ was indicated by comparing spectra obtained by using CH_4, H_2O, and D_2O (separately) as reactant gases, thus avoiding synthesis of an isotopically labeled compound. With more complex amino acids the $(QM\text{-}H_2O)^+$ ion becomes an important one, along with $(QM\text{-}NH_3)^+$ and $(QM\text{-}RSH)^+$.

The various known uses of CIMS were demonstrated with 29 alkaloids.[5,6] Alkaloids always give a QM^+ ion, and it is always of greater relative intensity than the M^+ ion of the corresponding EI spectrum. For alkaloids lacking aliphatic functional groups, the especially stable QM^+ ion forms the base peak, and sometimes as few as two fragmentation ions appear. For this type of alkaloid CIMS serves mainly to confirm the identity of the molecular ion. In more complex alkaloids, identification of hydroxyl and methoxyl groups is always possible due to the appearance of $(QM\text{-}H_2O)^+$ and $(QM\text{-}CH_3OH)^+$ ions. Skeletal information from rearrangements is generally absent. In the case of ephedrine, 1, whose EI spectrum furnishes no M^+ ion, the CI spectrum alone would suffice as a complete structure proof by supplying the molecular weight ($QM^+ = 166$), $(QM\text{-}H_2O)^+$, $(QM\text{-}CH_3NH_2)^+$, $(CH_3CH{=}NHCH_3)^+$, m/e 58, and $(C_6H_5CH{=}OH)^+$, m/e 107, which reassemble to give the structure.

The proposed structure of the antibiotic botryodiplodin, 2,[7] rests on physical methods, with CIMS as the main basis. A reliable spectrum could not be obtained using EIMS, but the CI spectrum showed the molecular weight to be 144; the elemental composition, $C_7H_{12}O_3$ (resolution: 10,000); and the functional group, hydroxyl, by ions at m/e QM^+, and $(QM-H_2O)^+$, among others. Additional guidance as to structure and stereochemistry was obtained from ir and nmr data. Using the structure then proposed, a mechanism was rationalized for some of the observed fragmentations.



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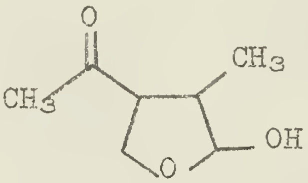

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THE SYNTHESIS OF GIBBERELLINS

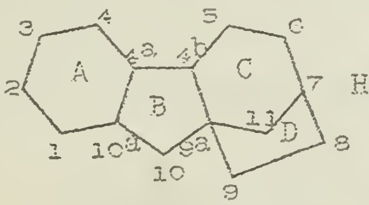
Reported by Anthony J. Playtis November 9, 1970

Gibberellins[1] are important phytohormones present in all higher plants. More than twenty naturally occurring gibberellins have been isolated and characterized.[2,3] All have the polycyclic gibbane system as a basic structure. The C_{19} gibberellins, of which gibberellic acid is the most important, differ mainly in the type of functionalization found in the A ring, with the presence or absence of a C_7 hydroxyl group being another very important distinction. The C_{20} gibberellins are similar, with the additional carbon atom at the 4a position. Highly labile, gibberellins undergo a wide variety of degradations and rearrangements under mild conditions. Important modes of degradation include the aromatization of the A ring, the Wagner-Meerwein rearrangement of the C and D rings, and the epimerization of the 4b proton. The high reactivity of this strained ring system coupled with its seven asymmetric centers has presented synthetic chemists with a challenge which they have yet to meet in a satisfactory manner.

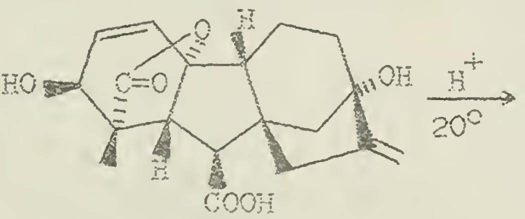
Early efforts were directed toward the synthesis of the immediate degradation products of gibberellic acid, which by virtue of their aromatic A rings have four fewer asymmetric centers and no lactone ring, thus greatly simplifying the synthetic task. The first success achieved was the synthesis of (±)gibberone, a relatively simple decarboxylated compound, by two groups.[4,5] Soon after, Loewenthal and Malhotra[6] produced (±)-gibberic acid. Using the same substituted indane as an intermediate,[7] Mori, Matusi and Sumiki[8,9] obtained (±)-epigibberic acid. By modifying the final steps in their synthesis, they were also able to synthesize (±)-gibberic acid, (±)-gibberone, and (±)-dehydrogibberic acid.[9] In all the above syntheses, the basic approach was to start with an indane which could lead, via a Robinson ring annelation, to a hexahydrofluorene with substituents that would enable closure of the D ring.

Using (±)-epigibberic acid as a starting material, Mori, et al.[10] next tackled the problem of actually synthesizing a gibberellin. They did indeed manage to produce (±)-gibberellin A_4, but to accomplish the formidable tasks of elaborating the A ring, rearranging the C and D rings, and obtaining correct stereochemistry and functionality, their synthesis wanders through a large number of low yield steps, thus making it elegant, but impractical. Indeed, completion of the entire sequence was only possible because many relay compounds could be obtained as degradation products of commercially available gibberellins. Gibberellins A_2, A_9, and A_{10} can be obtained from A_4;[11-13] thus, the work also constitutes a formal synthesis of these compounds.

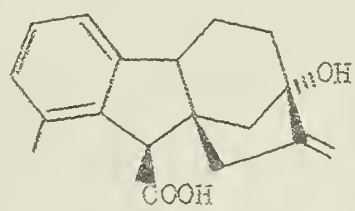
Nagata and his coworkers[14] have succeeded in synthesizing (±)-gibberellin A_{15} by using an intermediate which they had previously prepared in their syntheses of aconite alkaloids.[15] Once again, a large number of steps and moderate yields result in a very low overall yield.



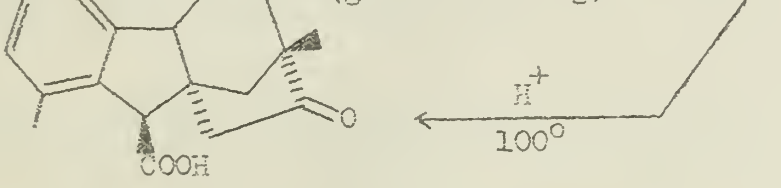
gibbane system



gibberellic acid
(gibberellin A_3)



allogibberic acid
(4b H is α)
epiallogibberic acid
(4b H is β)



gibberic acid
(4b H is α)
epigibberic acid
(4b H is β)

The above syntheses are the only ones that can be considered completely successful. However, many other workers have succeeded in synthesizing gibbane and fluorene systems of theoretical or synthetic interest.[16-31] Included in these studies are efforts to duplicate the biosynthetic route to gibberellins, which involves contraction of the B ring of kaurenoid type precursors.[16-19,32] Also, pioneer studies have been made to find possible synthetic routes to the A ring lactone system[20,21,33,34] and the substituted bicyclo[3.2.1]octane system[22-24,35,36] that makes up the C and D rings.

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RECENT MECHANISTIC EVIDENCE FOR THE STEVENS REARRANGEMENT

Reported by Ronald P. Taylor November 16, 1970

INTRODUCTION

The Stevens Rearrangement is the base-catalyzed [1,2] alkyl migration from nitrogen to carbon. The rearrangement was first observed in 1928 by T. S. Stevens and his coworkers[1] when they warmed an aqueous alkaline solution of phenacylbenzyldimethylammonium bromide (1).

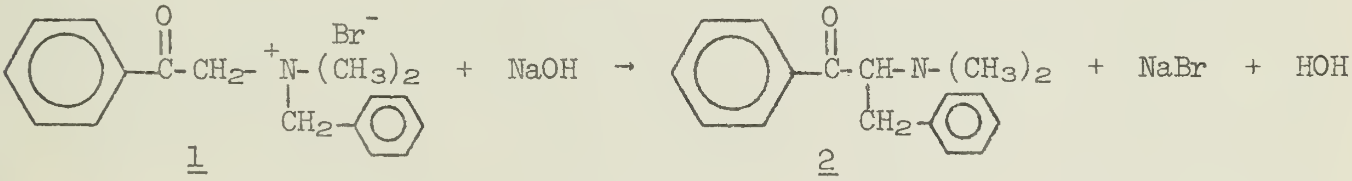
EXPERIMENTAL PROCEDURES

The usual conditions for the rearrangement are treatment of the ammonium salt with aqueous sodium hydroxide,[1] sodium alkoxide in alcohol,[2] sodamide in liquid ammonia,[16] phenyllithium in benzene,[32] or alkyllithium in alkane. The rearrangement product is usually isolated in high yield by extraction, column chromatography, or thin layer chromatography.[32]

THE SCOPE AND LIMITATIONS OF THE REARRANGEMENT

The Stevens rearrangement is by its nature rather limited structurally. It requires a quaternary ammonium salt containing at least two activated α-positions. Common migrating groups are benzyl,[1] allyl,[24] α-phenylethyl,[8] benzhydryl,[3] and 9-fluorenyl,[3] although recently several aryl groups have been reported to migrate.[26,37] Common recipient groups are phenacyl,[1] allyl,[24] acetonyl,[4] acetaldyl,[14] and benzyl.[5] In addition to the normal Stevens [1,2] migration, there have also been observed Stevens-type [1,3],[14,19,28] [1,4],[12,16,18,24,32] [1,5],[12] and [1,6][32] rearrangements. The present discussion will be limited to the [1,2] rearrangement and to the [1,4] rearrangement to the extent that it provides evidence for the mechanism of the [1,2] rearrangement.

Recently, the Stevens rearrangement has been utilized in determining the absolute configuration of an important spiro quaternary ammonium salt 3[27] in preparing models for an alkaloid study 4,[32] and in preparing an interesting new aromatic compound 5.[33]



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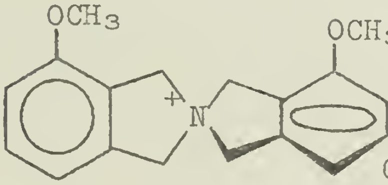

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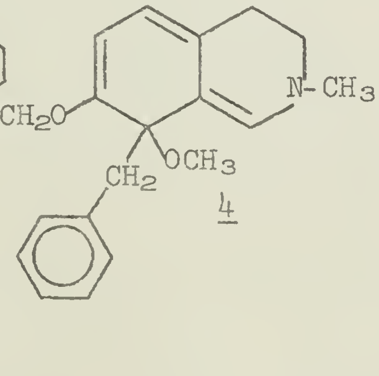

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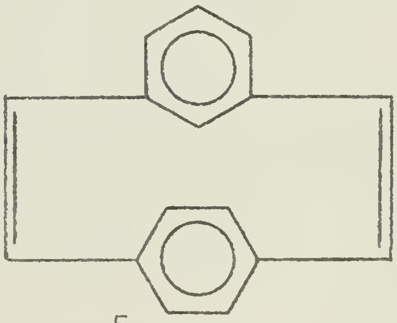


5

MECHANISM

Traditionally, there have been two mechanisms postulated for the Stevens rearrangement: an internal nucleophilic displacement or S_Ni reaction, and an intimate ion pair mechanism. The evidence for each will be discussed briefly before the recent mechanistic evidence is presented.

The Stevens rearrangement was early postulated to be intramolecular. The reaction follows 1st order kinetics in concentration of ammonium salt,[3] mixtures of differently substituted salts give no cross products,[3] and externally added labelled benzyl ion is not incorporated into the product.[20] Stereochemical evidence, to be discussed later, is also consistent with an intramolecular mechanism.

Early kinetic measurements[2,3,6] were consistent with an ion pair mechanism, via an α-ylide 7, in which the benzyl group migrates as an anion. (Fig. 1). Electron-withdrawing benzyl substituents were observed[3] to accelerate the reaction, presumably by stabilizing the anion with respect to the ylide. The magnitude of acceleration was later interpreted[11] to indicate the development of a full negative charge on the benzyl group in the transition state; i.e., to indicate ion pair formation rather than nucleophilic displacement. Electron-withdrawing phenacyl substituents were observed to have only a very small decelerating effect on the rate, which was interpreted[2] to indicate stabilization of the substrate cation with respect to the ylide.

In 1947, it was observed that the rearrangement gives 97-98% retention of optical activity,[8] and later that the configuration about the migrating carbon atom was retained,[10] not inverted, based on the known configurational relationship of ℓ-N,N-dimethyl-α-phenylethylamine and ℓ-β-methylhydrocinnamic acid. The retention of optical activity was interpreted[9] as evidence for an internal nucleophilic displacement (S_Ni) mechanism, rather than the ion pair mechanism. However, the observation in 1962 of predominant retention of[16] configuration for both [1,2] and [1,4] shifts in an optically active α-phenylethylallylammonium salt supported the ion pair mechanism over the S_Ni mechanism.

Mechanistic theories have changed quite dramatically since 1967. LCAO-MO calculations[20,45] indicate that the transition state for a cyclic concerted alkyl shift is only 0.11 β unit endothermal to the reactant because of a favorable charge distribution between nitrogen and carbon in the transition state. The concerted process is therefore favorable from an energetic standpoint. However, such a process is known[39,40] to require the conservation of orbital symmetry. An application of the Woodward-Hoffmann rules showed that the [1,2] rearrangement is symmetry-allowed only with inversion of configuration at the migrating asymmetric center. The experimental result for the [1,2] shift is contrary to the symmetry restrictions and thus cannot be a concerted process. However, Woodward and Hoffman have suggested[38] that there is possibly some strong interaction between available alkali metal orbitals and the orbitals of the ylide to make the [1,2] shift with retention of configuration the symmetry-allowed process. A later examination[36] showed that the metal has no effect on the course of the reaction.

Systems containing allyl groups 10 had previously been reported[16-18] to give mixtures of both symmetry-allowed [1,4] products 12 and symmetry-forbidden [1,2] products 11, Fig. 2. However, a re-examination[23] of these reactions has shown that only the symmetry-allowed products 12 were formed, and that a later thermal rearrangement converted the [1,4] products to identical products 11 expected for a [1,2] rearrangement. This explanation may account for the observation of symmetry-forbidden [1,2] products in allyl systems, but obviously cannot account for their formation in non-allylic systems.

An NMR analysis of the product 18 of the reaction of benzyne 13 with N,N-dimethylbenzylamine 14 showed evidence[21] of chemically induced dynamic nuclear polarization. This observation is an indication of a radical as a direct product precursor.[41-44] The reaction sequence of Fig. 3 was postulated.

The observation of a CIDNP effect in a system closely analogous to the Stevens rearrangement suggested that it may proceed through a radical pair mechanism, rather than an ion pair or S_Ni mechanism.

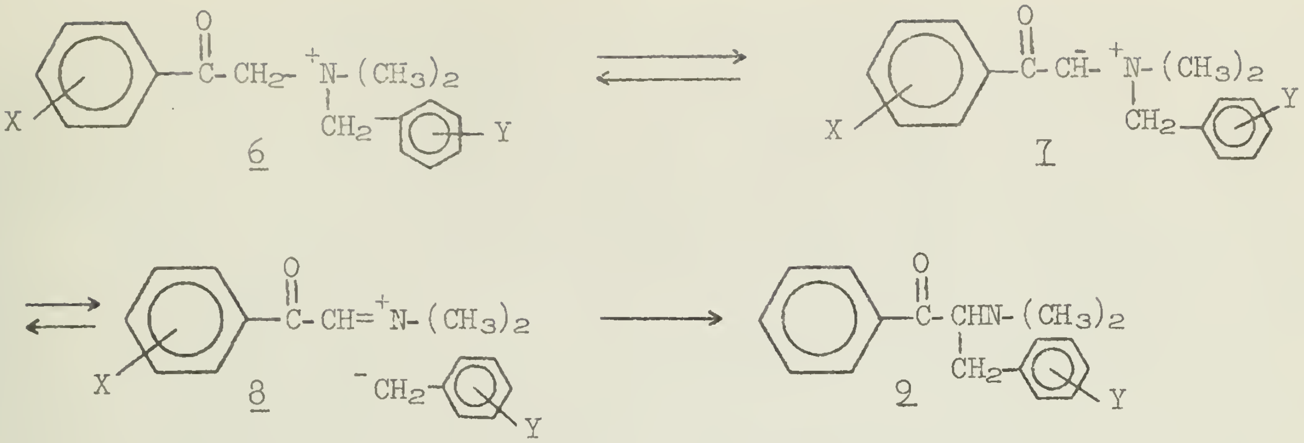


Fig. 1. Ion Pair Mechanism

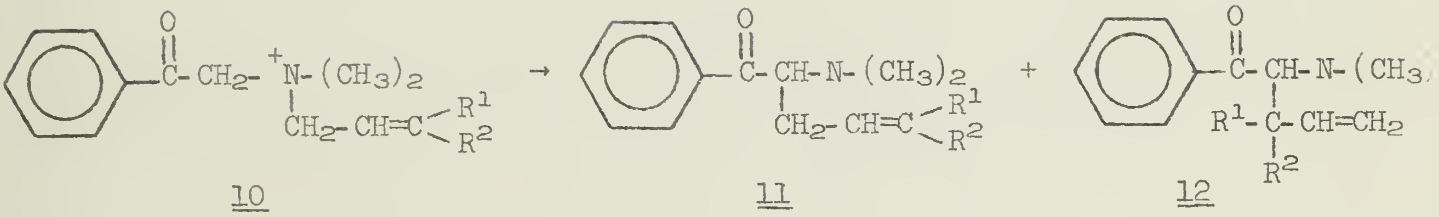


Fig. 2

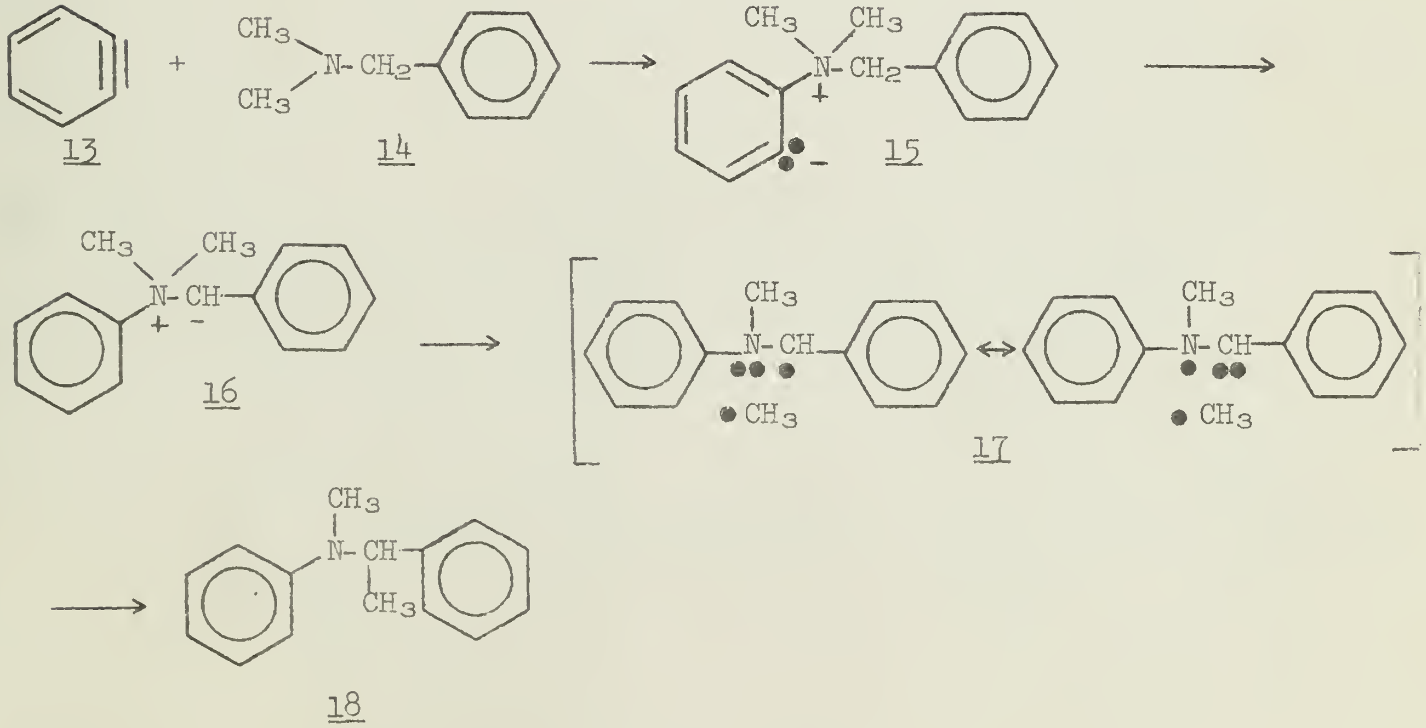
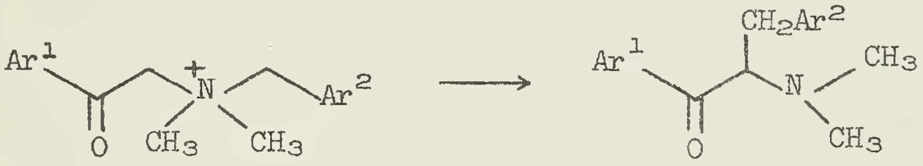


Fig. 3. Radical Pair Mechanism

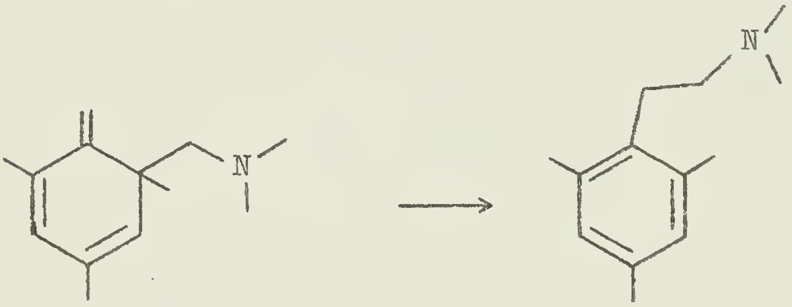
The rearrangement of 1 was re-examined[22] and an NMR spectrum of the reaction mixture showed a definite CIDNP effect at the Benzylic proton of the product. Since that time, there have been observations[36] of CIDNP effects for [1,2] shifts in several similar systems (19 → 20 in Fig. 4), in a Stevens-type [1,3] rearrangement[28] (21 → 22), in several Stevens-type ammonio-amidate rearrangements[25,34] (23 → 24), in a Stevens-type rearrangement of a Sulfur ylide[30] (25 → 26), and in a Stevens-type rearrangement of an acetylenic ammonium ion[31] (27 → 28). CIDNP effects have not been observed in [1,4] rearrangements, consistent with their being symmetry-controlled concerted processes.

Several cautions[35] on the interpretation of CIDNP effects should be mentioned. Since relatively minor pathways may give rise to observable CIDNP signals, precautions must be taken to insure that neither a minor side reaction nor reversible polarization of the product is responsible for the observed CIDNP signal. It is not yet clear whether the necessary precautions have been taken in the very recent studies.

Finally, a system has been studied[34] in which the nature of a substituent controls the mechanism of a Stevens-type rearrangement (29 → 30 → 31, 32). If R_1 is H or CH_3, no CIDNP signal can be detected and the product (31) of a symmetry-controlled concerted process is obtained. However, if R_1 is Ac, the transition state of a concerted process would require an unfavorable orthogonal geometry of allyl and acetyl groups, so that the concerted process is inhibited and the alternate nonconcerted process to give product is permitted. NMR examination of the product of this pathway showed a CIDNP effect, supporting its radical origin.



19 20



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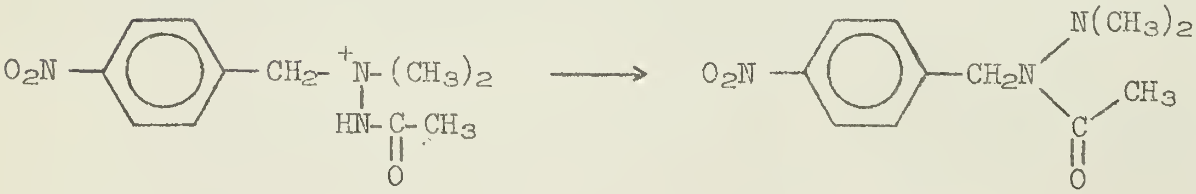

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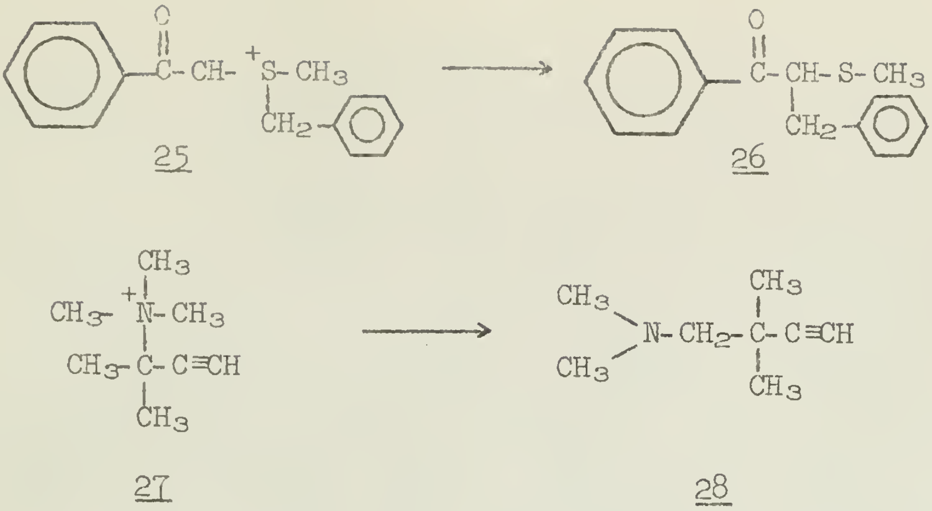
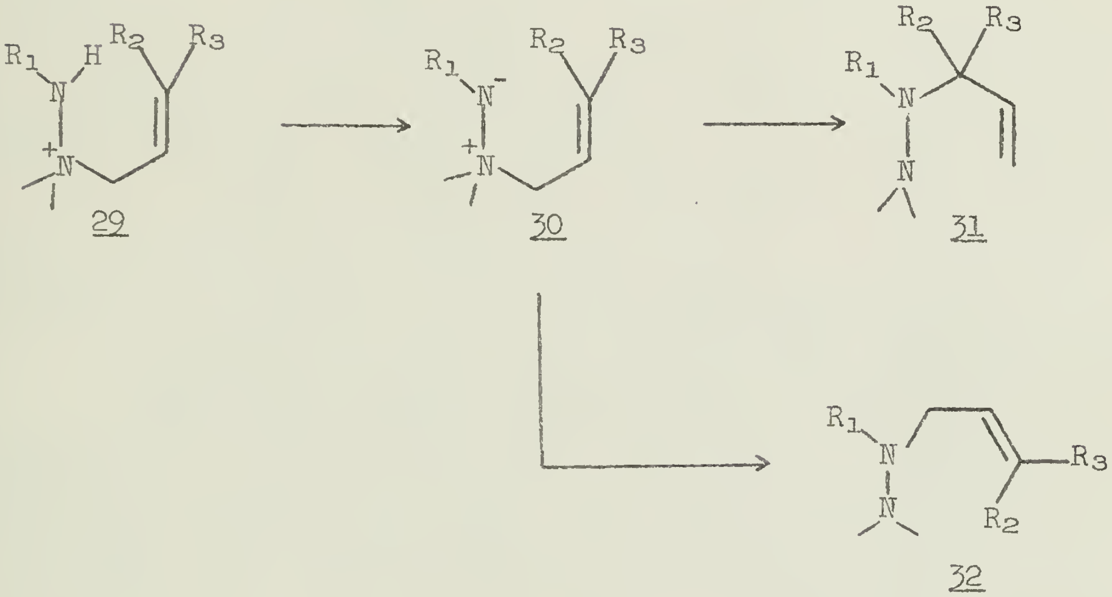


Fig. 4. Stevens-type systems in which CIDNP effects have been observed.



CONCLUSION

The traditional mechanisms for the Stevens rearrangement seem to have been questioned by recent evidence. The available information is now consistent with a concerted symmetry-controlled mechanism for the Stevens [1,4] rearrangement, and a nonconcerted mechanism via a radical pair for the Stevens [1,2] rearrangement.

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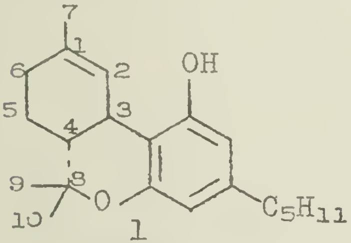
RECENT DEVELOPMENTS IN THE CHEMISTRY OF HASHISH CONSTITUENTS

Reported by James A. Bradshaw November 19, 1970

The chemistry of the secondary metabolites of _Cannabis sativa_ L. has received much attention due to the unique psychotomimetic properties of the plants constituents. The flowering part of the female of the plant excretes a resin which contains a number of compounds depending on the variety (indica or non-indica). As much as 1.2% of these compounds contain the active constituents. Mechoulam and Gaoni have proposed the term cannabinoids[1] for the C_{21} compounds of _C. sativa_, more commonly called hashish in Europe and Asia, and marihuana in North America. Because of the widespread drug use of these compounds, there has been increasing interest in their physiological and psychological effects in humans. The structure elucidation and synthesis, along with the physiological implications of the problem, have been subjects of many review articles.[1-3] A recent seminar has covered the synthesis of the optically inactive constituents.[4] The purpose of the present seminar is to relate the recent developments in cannabinoid chemistry and physiology with emphasis on the synthesis of the optically active constituents.



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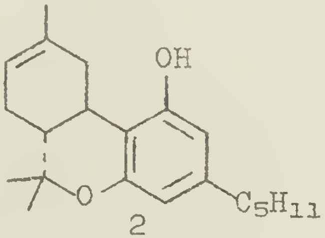
Δ^1-THC



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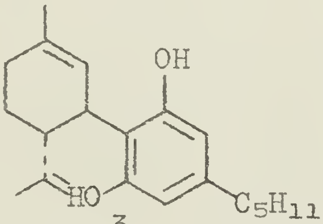
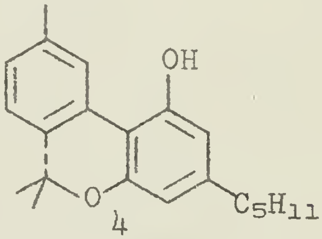
Δ^6-THC



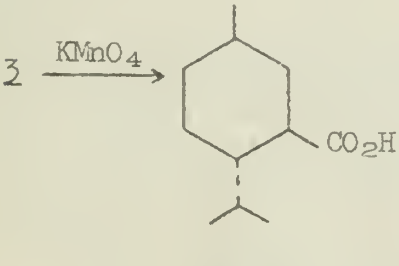
3
cannabidiol



4
cannabinol

STRUCTURE OF THE NATURALLY OCCURRING CANNABINOIDS

The major naturally occurring cannabinoids are given above. The group is by no means complete for over twenty compounds have been identified.[2] The major active constituent is 3,4-_trans_-Δ^1-tetrahydrocannabinol (THC) (1). Isolation and identification of this and the other compounds go back to as early as 1840, but is was not until 1895 that the first compound, cannabinol, was isolated. The next major constituent isolated was cannabidiol, whose structure was determined by Adams.[5] Adams also determined the stereochemistry about the 3,4 position and the absolute configuration of the natural cannabinoids through structure degradations of tetrahydrocannabidiol[6] to yield menthane carboxylic acid (5). Conversion of 5 to the anilide and comparison of melting point and optical rotation with the anilide prepared from D(-)-menthol places the natural cannabinoids in the D series relative to glyceraldehyde. The optically active natural cannabinoids are levorotatory.



5

The positioning of the double bond in Δ^1-THC was not determined until 1964 with the help of nmr and mass spectral analysis.[7-10] More recently, conformational analysis using Westheimer calculations, along with proton magnetic resonance observations of nuclear Overhauser effects were determined for cannabinol and (-)-Δ^1-THC.[11]

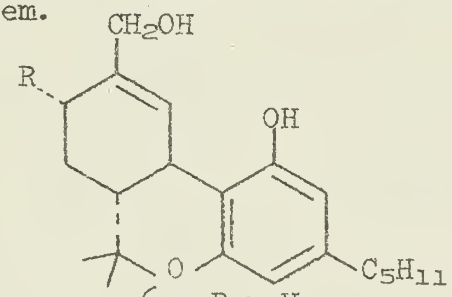
PHYSIOLOGY AND METABOLISM

Marihuana, which may be taken orally or, more commonly, smoked, has many and varied effects on the central nervous system. Among these are elevation of the pulse rate and blood pressure, dilation of the pupils and sensitivity of the eyes to light, lassitude, and increased thirst and hunger. The more psychological effects are alternating periods of happiness and depression, and paranoia.[3] Of the naturally occurring cannabinoids, only the Δ^1 and Δ^6 isomers have been found to be psychotomimetic. The Δ^1 and Δ^6 isomers also produce ataxia in man and animals and cannabidiol has been found to have some antibiotic properties.[1] There is also some recent, but unsubstantiated, evidence that the Δ^6 isomer is not psychotomimetic.[12]

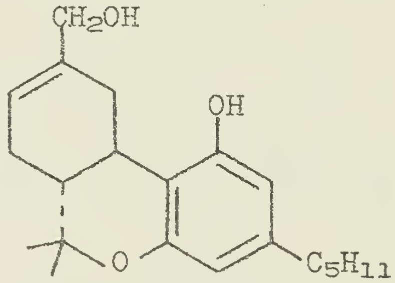
Earlier work was done with crude extracts from the plant and in many instances gave conflicting results. Due to lack of availability and purity very little reliable pharmacological work could be done until reliable synthetic methods could be developed. More recently, studies using the racemic Δ^1 and Δ^6 isomers on rhesus and squirrel monkeys were undertaken. The monkeys experienced hallucinations, depression and lack of desire or ability to perform complex tasks. In higher doses death resulted. The effects were not always short term, and lasted for periods of up to and over a week.[13]

Metabolic investigations have been undertaken using ^3H and ^{14}C labelled compounds.[14,15] Recently, metabolic studies were carried out using Δ^1-THC tritiated at the C_2 position.[16,17] When labeled compound was incubated with rat liver homogenates, 7-hydroxy-Δ^1-THC (6a), (30%) and 6,7-dihydroxy-Δ^1-THC (6b) (30%) were isolated and identified by nmr and mass spectral analysis. It was found that 6a was equally as active as 1, but 6b was inactive. In a similar study using rat liver homogenates, 7 was shown to be the major metabolite (65%) of 2 and was also synthesized from 2. Pharmacological tests in rats showed 7 to have effects similar to those of 1 and 2.[18] Work has also been done using tritiated 2 in rabbits.[19] Urine analysis showed the metabolite to be a hydroxylated derivative of 2 and synthesis proved it to be identical with 7.[20]

It is also not known whether the active constituents will have the same physiological effects in humans as in animals. Work is also being done on the chemistry of the iso-THC's such as 12, and some of the other synthetic cannabinoids.[21-29] Hopefully adequate physiological testing may shed light on the problem.



6a, R = H
6b, R = OH

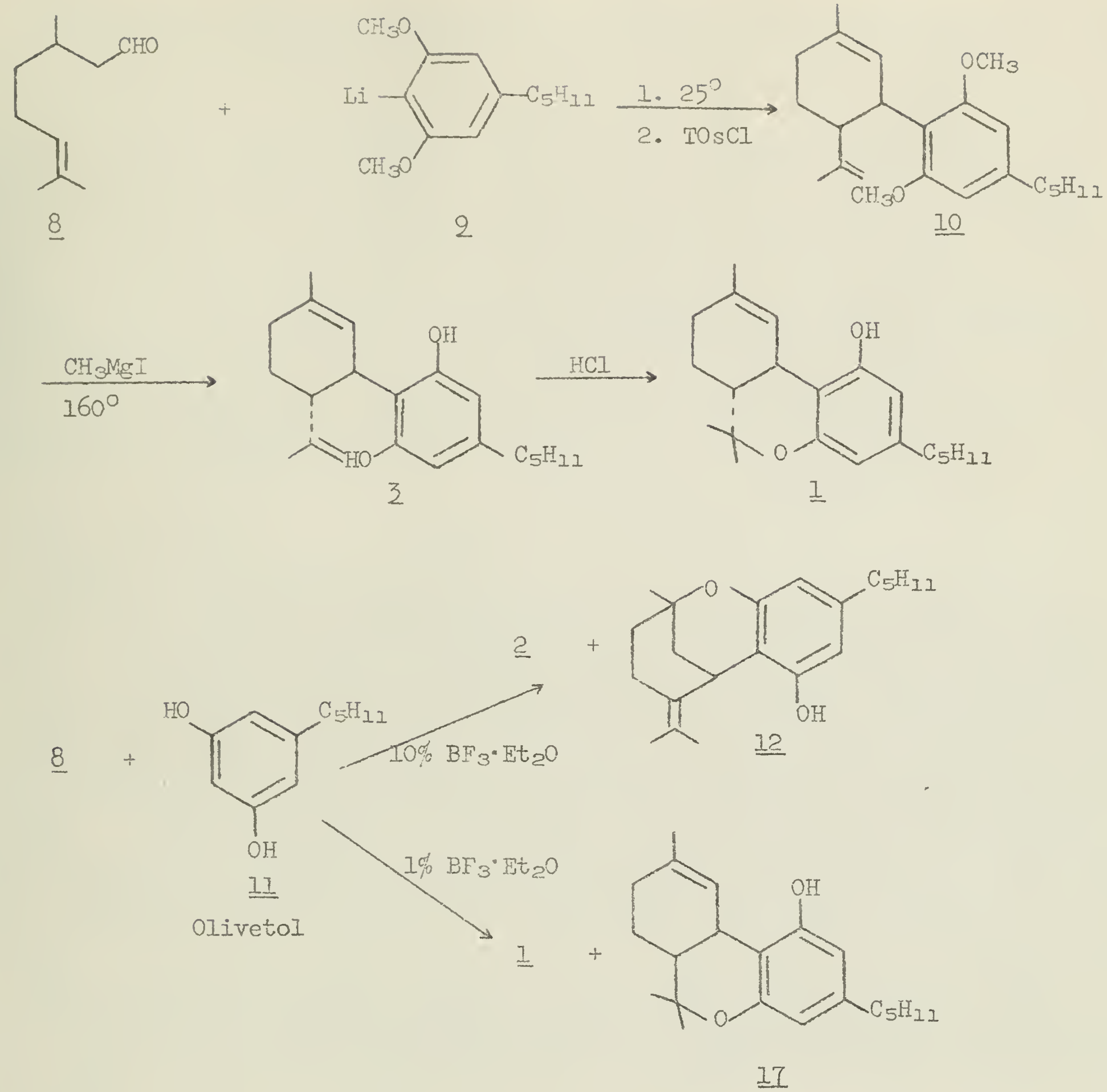


7

SYNTHESIS OF OPTICALLY INACTIVE CONSTITUENTS

The first total synthesis of optically inactive 1 and 3 patterned after the suggested biogenetic pathway, was achieved by Mechoulam and Gaoni in 1965.[30] It consists in the condensation of citral "a" (8) with the lithium salt of the olivetol derivative 9 to give 10, then reaction with methyl magnesium iodide[31] followed by cyclization to give dl-1. The overall yield to 1 was 2%.

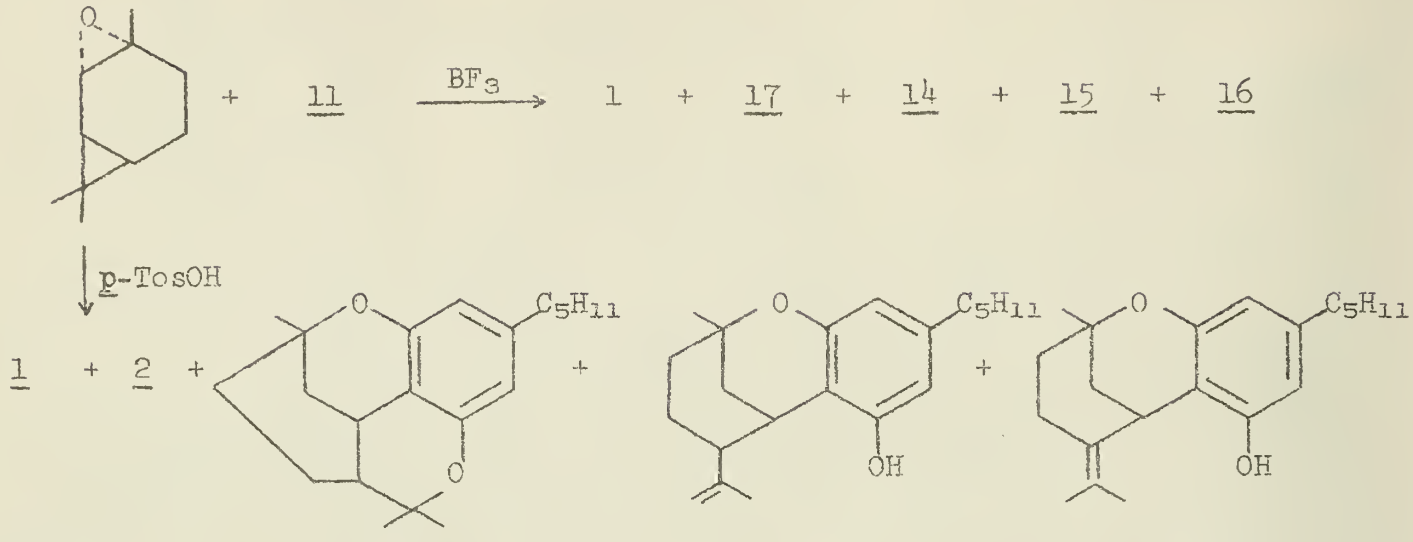
Under slightly different conditions, using 10% boron trifluoride etherate in benzene, Taylor and his co-workers were able to synthesize Δ^6-THC in 10-20% yield, contaminated, however, with some iso-THC derivative (12). Using 1% boron trifluoride etherate in methylene chloride, Mechoulam and Gaoni prepared Δ^1-THC in 20% yield along with cis-Δ^1-THC (17).[32]



SYNTHESIS OF OPTICALLY ACTIVE CONSTITUENTS

Razdan and Handrick have recently developed an acid catalyzed stereospecific synthesis of (-)-3,4-trans-Δ^1-tetrahydrocannabinol.[33] By condensing olivetol (11) with equimolar amounts of (+)-trans-2-carene oxide (13) in benzene with p-toluenesulfonic acid as the catalyst. A mixture of products was obtained and analyzed by glpc. The mixture contained 23% Δ^6-THC, 7% Δ^1-THC, 13% cytrillidene cannabis (14), Δ^8-iso-THC (15), and 11% iso-THC (16). After chromatographic workup on Florisil, (-)-Δ^6-THC was obtained. Optical rotation indicated an optical purity of roughly 95%. If the molar ratio of 13 to 11 was increased to 1.6, (-)-1 was formed in higher yield (28%), along with 17 and other products. However no (-)-Δ^6-THC was observed.

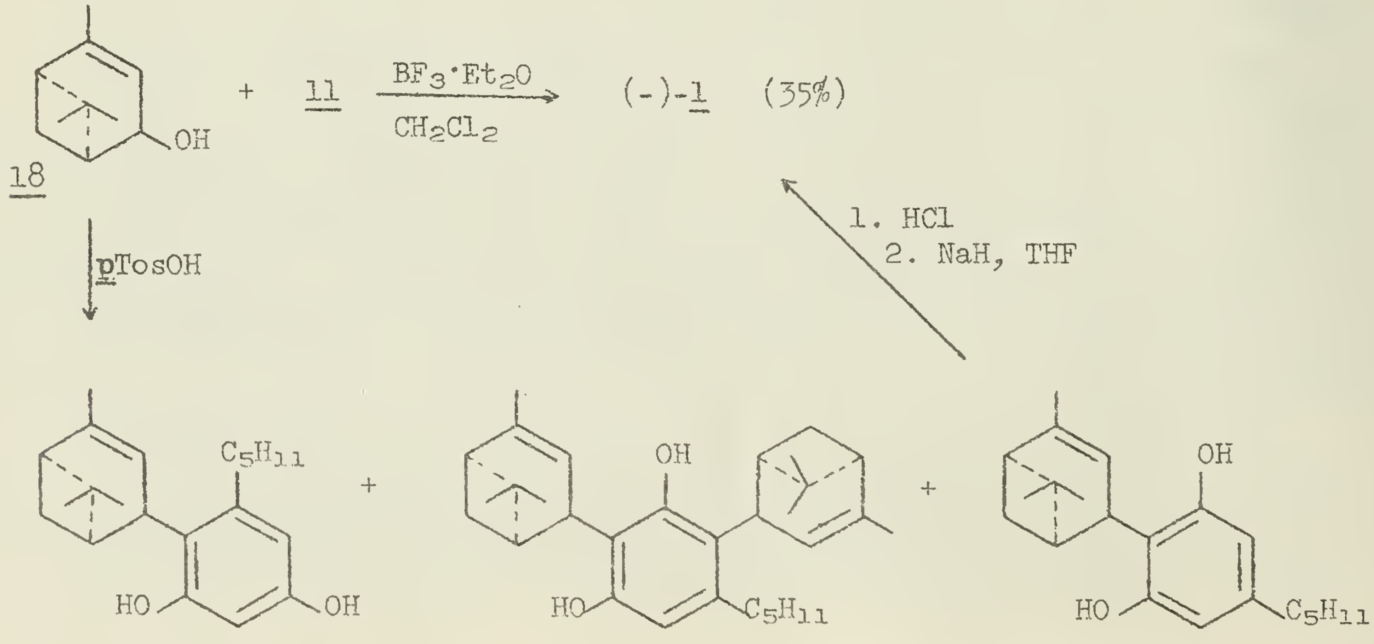
In a similar experiment using the non-protonic acid boron trifluoride etherate (1% in methylene chloride), a mixture of 1 and 17 was obtained in the ratio 60:40. After separation by glpc, ORD showed the optical purity of (-)-Δ^1-THC to be greater than 80% by comparison with an authentic sample. A proposed mechanism can be postulated through initial formation of 1 and 17 followed by acid catalyzed rearrangements to 14, 15, and 16.[24,28]



14 15 16

A similar synthesis, which also gives approximately 97% optical purity of the Δ^6 isomer has been reported by Mechoulam, Gaoni and Braun.[34] (-)-Verbenol (18) and olivetol were condensed in the presence of p-toluenesulfonic acid to give a mixture of three products, which was separated by chromatography. The major products were believed to be 4-trans-(2-olivetyl)pinene (19) (45% yield), the isomeric olivetylpinene (20) (20%), and the double addition product 21 (15%). In the presence of boron trifluoride etherate in methylene chloride at room temperature for ten minutes, compound 19 was converted into the Δ^6-THC isomer in 85% yield. Other products were not reported. Optical purity based on optical rotation was 97%. It was also found that 18 and 11 could be converted directly to the (-)-Δ^6-isomer in 35% yield using boron trifluoride etherate. In the initial reaction of 18 and 11, with either acid catalyst, no cis isomer was formed.

The Δ^6 isomer was converted to the Δ^1 isomer by addition of dry hydrogen chloride in the presence of zinc chloride in a Markownikoff manner, followed by dehydrohalogenation with sodium hydride in refluxing tetrahydrofuran. This gave a mixture of (-)-1 in 55% yield and (-)-2.

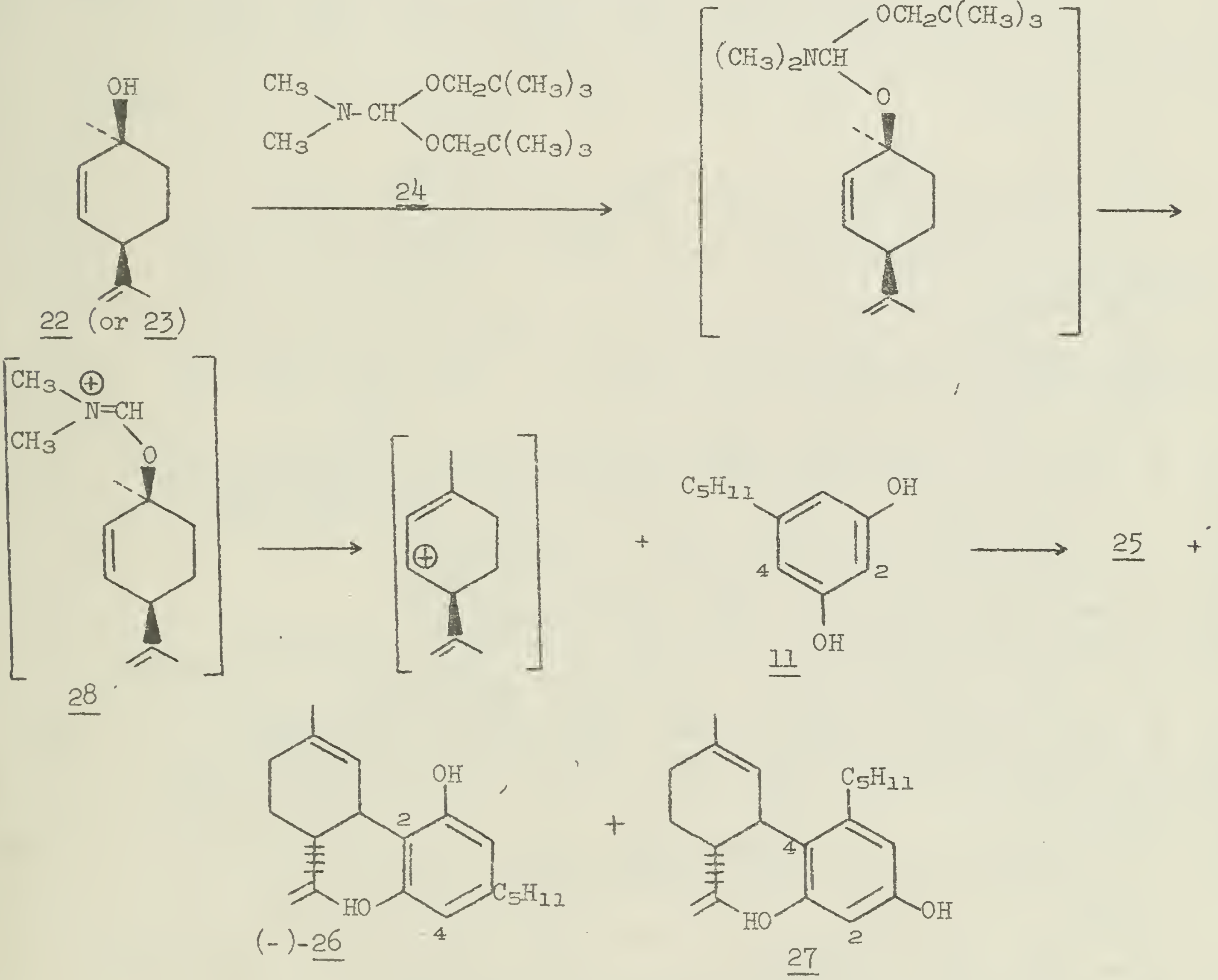


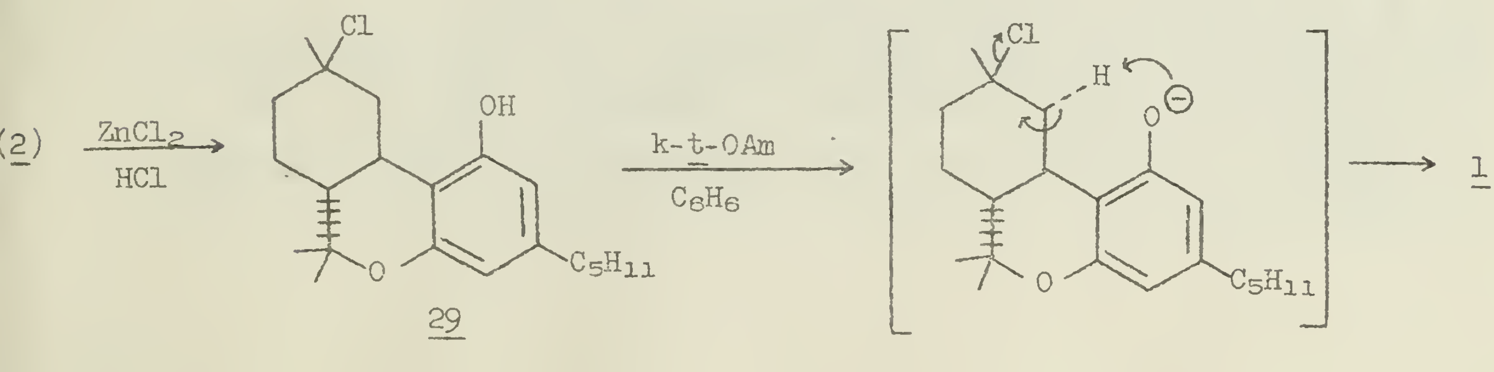
18 20 21 19

Petrzilka, Eschenmoser and their co-workers[35-38] have described the synthesis of a number of optically active cannabinoids. Thus, (+)-*cis*-(22) or *trans*-*p*-menthadien(2,8)-1-ol (23) was condensed with olivetol in the presence of N, N-dimethyl dineopentyl acetal (24) to give a mixture which contained the 2,4 diadduct of olivetol (25) (5%), (-)-cannabidiol (26) (25%), and the cannabidiol isomer 27 (35%). The reaction proceeds through the intermediate iminium ion 28 ,[39,40] followed by attack of olivetol in a stereospecific manner to yield optically active products.

The same reaction was also run using weak acids, among them (24), picric, maleic, and oxalic acids. It was found that all gave higher ratios of the undesired adduct 27 , with 24 giving the highest yield of cannabidiol. If a strong acid such as *p*-toluenesulfonic acid or trifluoroacetic acid was used, the reaction proceeded directly to the Δ^6-isomer in 53% yield.

A new method for the conversion of 2 to 1 was also developed: the treatment of 2 with Lucas reagent to give 29, followed by treatment with potassium *t*-amylate in benzene to produce 1.





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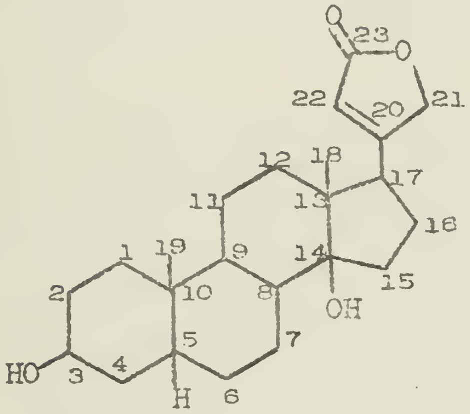
SYNTHETIC APPROACHES TO BUFADIENOLIDES

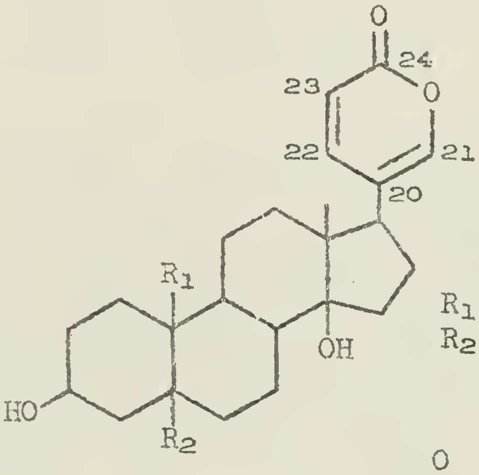
Reported by James A. Basso November 23, 1970

INTRODUCTION

Certain natural steroidal lactones have been used in the medical arts for several thousand years, primarily because of their powerful action on the heart. The cardiac active steroids can be divided into two groups: cardenolides and bufadienolides. Cardenolides are characterized by a butenolide ring while bufadienolides contain an α-pyrone ring. Both types of compounds have the unsaturated lactone group in the 17β-position. Another prominent feature is the 14β-hydroxy group or a 14β-, 15β-oxido substituent. Some important members of this steroidal family are shown (1-6). These compounds are most commonly isolated from plants as glycosides and from toad venom. Generally toad venom bufadienolides occur as the free steroid or aglycone. While a large number of naturally occuring steroids have been synthesized, it is only within the past two years that the bufadienolides have yielded to total synthesis. The chemistry and attempted synthesis$^{1-3}$ have been reviewed several times in the past twenty years and more recently by Sondheimer.^{4} It is the purpose of this seminar to examine recent syntheses of the bufadienolides.

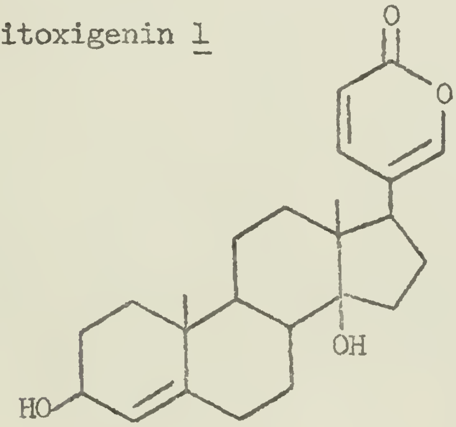


Digitoxigenin 1

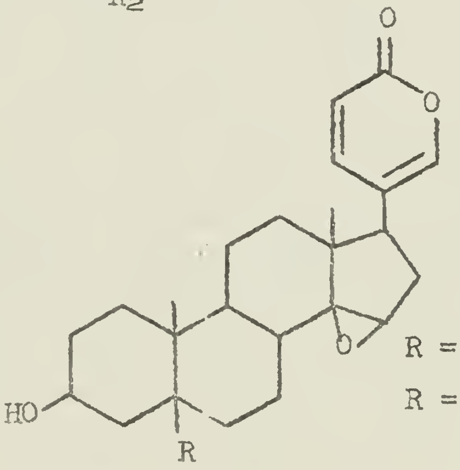


R_1 = CH_3 Bufalin 2
R_2 = H

R_1 = CHO Hellebrin 3
R_2 = OH



Scillaren 4



R = H Resibufogenin

R = OH Marinobufagin

HISTORICAL

The effect on the heart of extracts from the bulbs of the red and white squill has been known since 3,500 B.C.^{5} Small doses were found to stimulate a diseased heart, but excessive doses caused death by sudden contraction of the heart. Consequently the extracts have been used by primative tribes as arrow poisons and in trial by ordeal during the middle ages. The ancient Chinese developed a similar drug from toad venom or dried toad skin called Ch'an Su. It too found use as a cardiac stimulant but was largely supplanted by digitalis in the 18th century.

The bufadienolides were re-investigated with the pioneering work of Wieland[6] in 1913, who studied extracts from the common European toad, bufo vulgaris, and by Stoll,[7,8] who isolated and characterized a number of squill glycosides, primarily scillaren A. The structure of bufalin 2, a prime component of toad venom, had been determined by Kuwada[9] and confirmed by Meyer.[10]

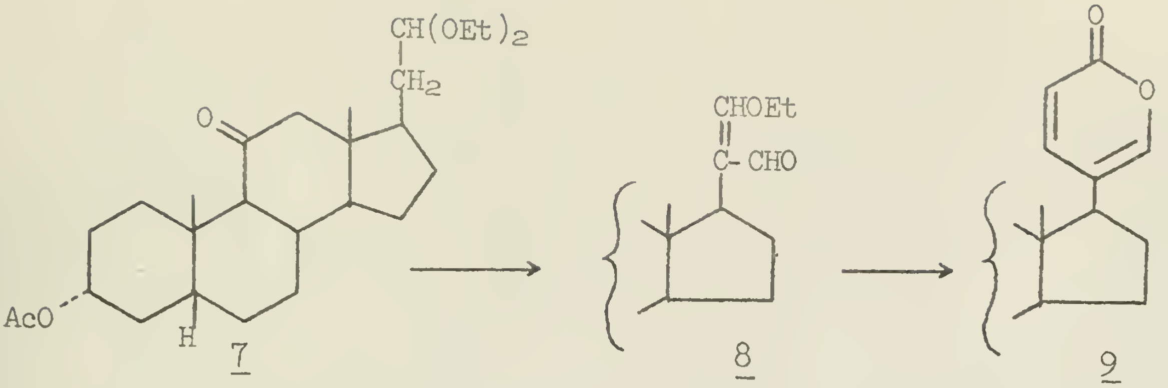
Interest in these steroids has been renewed in recent years with the finding that bufalin could be used as a local anesthetic,[11] but a more important discovery was that certain α,β-unsaturated lactones have antibiotic activity and selectively inhibit the growth of animal tissue.[12] Several workers[13-16] have attributed anti-tumor properties to a number of cardenolides and bufadienolides.

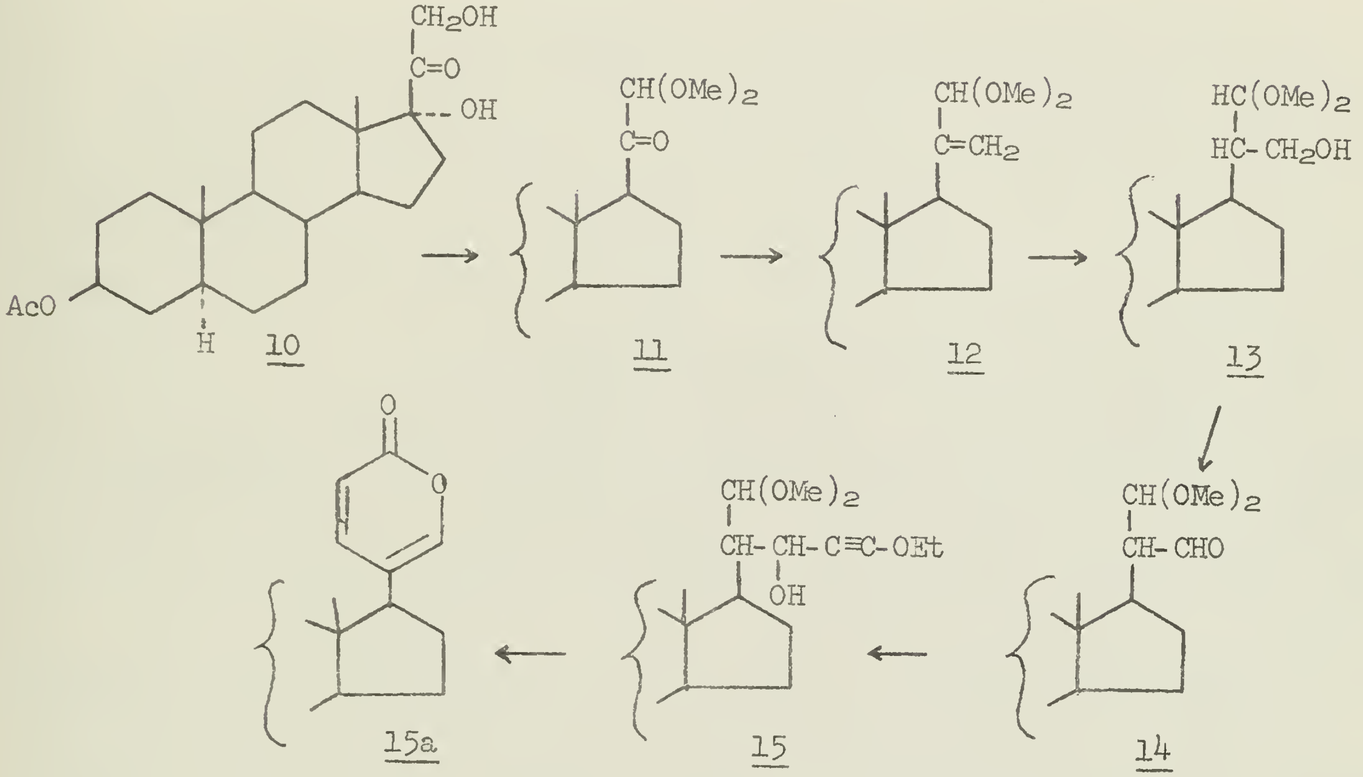
SYNTHESIS

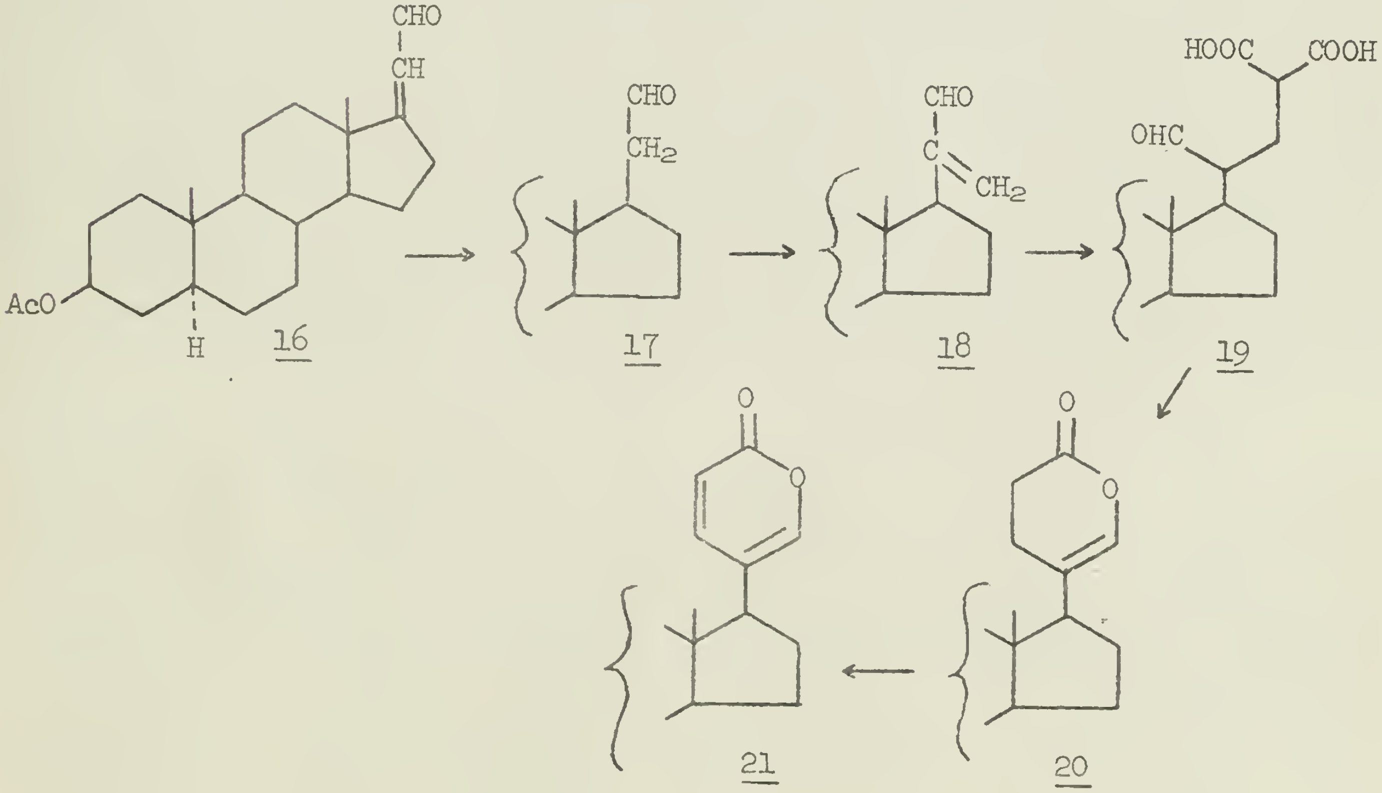
Synthesis of the cardiac active steroids as a class has presented considerable difficulty. It would appear that a 14β-hydroxy-20-keto steroid type could be prepared and the α-pyrone could then be constructed using standard methods. However, there are three main difficulties to this type of approach: (1) 14β-hydroxy steroids dehydrate readily in acid, and no adequate protecting group is known for this substituent, (2) the 17β-side chain is the less thermodynamically stable configuration and inversion may easily occur, (3) the 14β-hydroxy group can react with 20-keto steroids to form hemi-ketals.

In order to prepare the natural bufadienolides, methods for the introduction of the α-pyrone ring at the 17β-position had to be developed. Elderfield and coworkers,[17-19] working with model compounds developed a synthesis of 5-alkyl-α-pyrones; however, the method failed to be applicable to steroids. Little work was done in the field until 1961 when a preliminary report of the synthesis of a bufadienolide appeared.[20] The acetal 7 was treated with $POCl_3$-DMF in a Vilsmier-Haack reaction to yield dialdehyde enol ether 8, and this was followed by a Reformatsky reaction using ethyl bromoacetate to give 9. For the purpose of this discussion, reaction in which the 3-hydroxyl is protected will not be described unless it is of special interest. Also, in any reaction where conditions would remove the protecting group, it will be assumed that the position has been reprotected before proceeding to the next step in the sequence. A synthetic sequence reported by Sondheimer[4] started with the dihydroxyacetone derivative 10, which was converted to acetal 11 by treatment with HCl in methanol. Conversion of 11 in a Wittig reaction with methylenetriphenylphosphorane yielded 12. Brown hydration and subsequent chromium trioxide oxidation gave aldehyde 14. Treatment of this compound with lithium ethoxyacetylide produced 15. Ring closure was effected with boiling concentrated methanolic HCl to produce bufadienolide 15a. This method suffers from the extreme acid conditions in the final step which would preclude any attempt to prepare a natural bufadienolide with a 14β-hydroxy group present. It is difficult to evaluate this method due to the lack of experimental details.

Recent bufadienolide syntheses have been described by Engel,[21] Sarel,[22] and Stache.[23,25] Utilizing the known unsaturated aldehyde 16, Engel hydrogenated 16 to aldehyde 17 over $Pd/CaCO_3$ without reducing the aldehyde function. An aldol condensation with aqueous formaldehyde yielded 18 in about 77% yield. A Michael addition of diethyl malonate was followed by saponification to produce the dicarboxylic acid 19. Lactonization was accomplished with p-toluenesulfonic acid in refluxing benzene. Bufadienolide 21 was then prepared by dehydrogenation of 20 with selenium dioxide in about 34% yield. This method is quite practical in that the conditions employed would be suitable for the naturally occuring 14β-hydroxy derivatives. Sarel,[22]


CH(OEt)2
CH2
O
AcO
H
7
CHOEt
C- CHO
8
O
O
9


CH2OH
C=O
OH
AcO
H
10
CH(OMe)2
C=O
11
CH(OMe)2
C=CH2
12
HC(OMe)2
HC- CH2OH
13
CH(OMe)2
CH- CHO
14
CH(OMe)2
CH- CH- C≡C- OEt
OH
15
O
O
15a


CHO
CH
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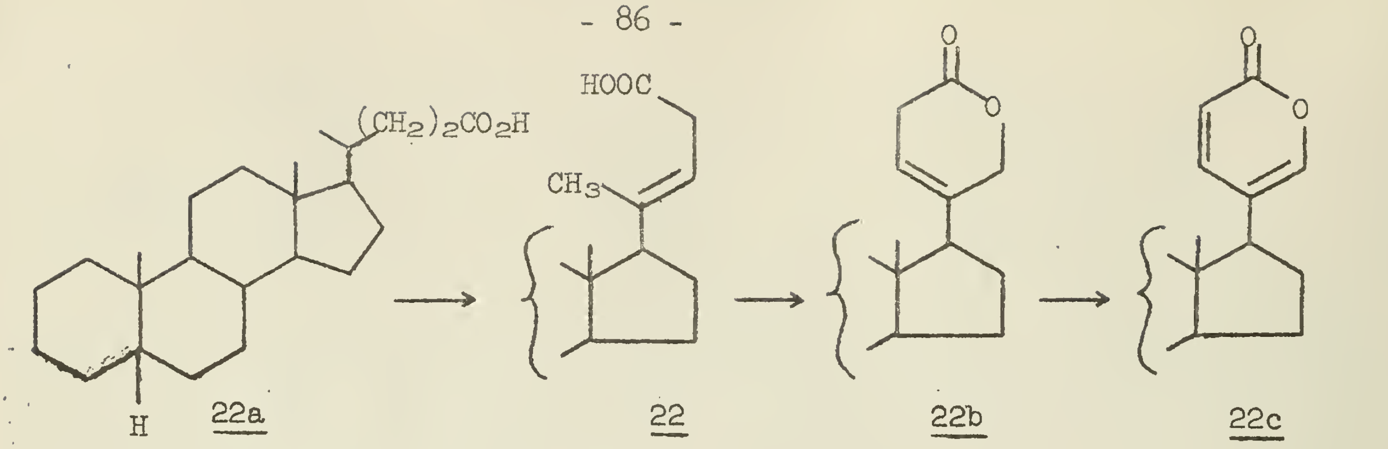
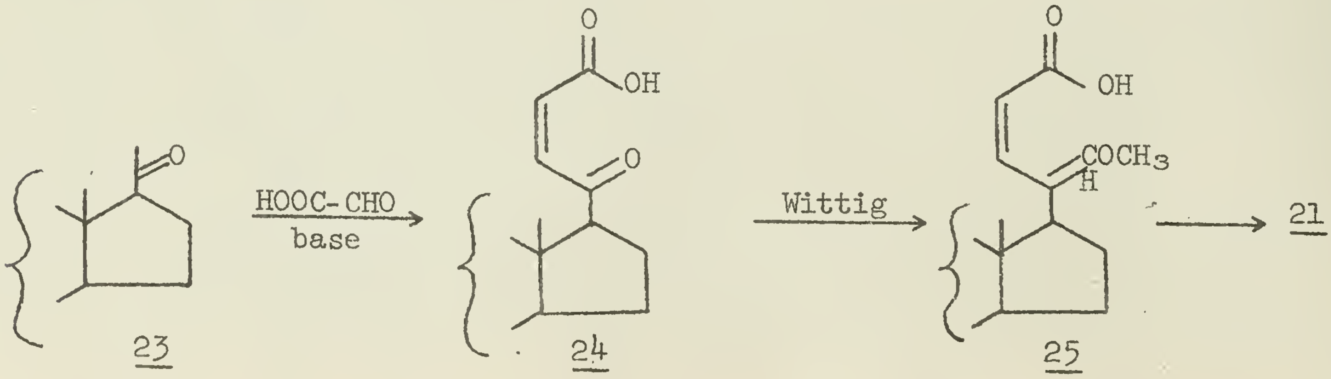
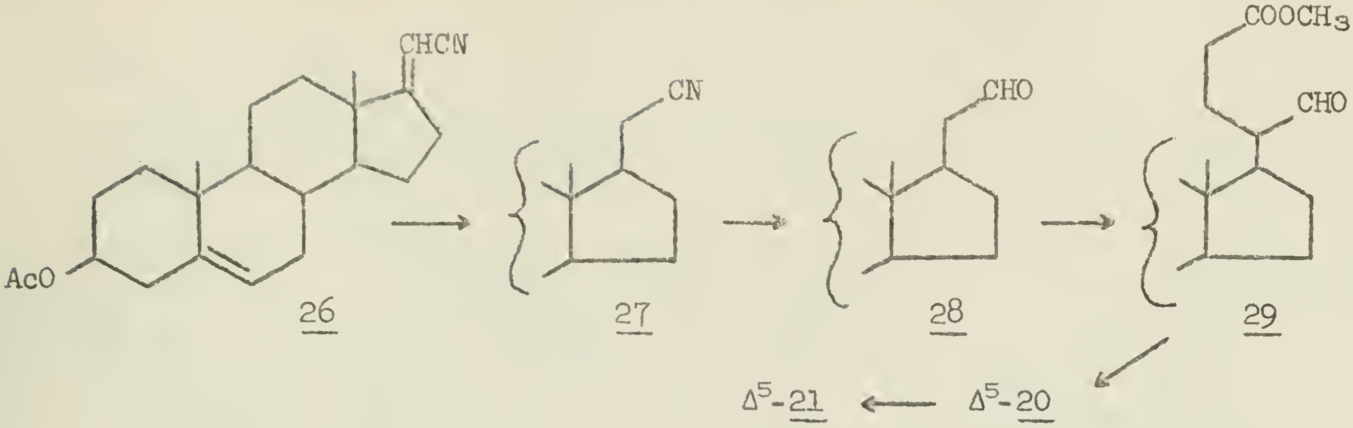


in a preliminary communication, reported a different method of dehydrogenation with 2,3-dichloro-5,6-dicyanoquinone (DDQ) to produce bufadienolides. Constructing compound 22 from the C_2 side chain of pregnane derivative 22a, he was then able to cyclize to the lactone by exposing 22 to N-bromosucinimide in carbon tetrachloride for 48 hours at room temperature. The product, 22b, was characterized by its nmr spectrum. Dehydrogenation was accomplished with DDQ in the presence of p-toluenesulfonic acid in dioxane. The dehydrogenation at C-22 proceeded quantitatively. Engel[21] and Pettit,[30] however, report that dehydrogenation with this reagent in their systems, which differed only in being a 5α-pregnan-3β-acetate, proved unsuccessful.

In a series of papers[25-31] Pettit has described additional routes not only to the bufadienolides but also to the cardenolides. His original approach involved the aldol type coupling of a 20-keto steroid with glyoxylic acid based on a procedure developed by Newman,[32] followed by reaction with a suitable Wittig reagent to produce an intermediate such as 25. The lactone could then be formed by a variety of reagents. This particular scheme was unsuccessful at a number of steps, most notably, the failure of the Wittig reagent to produce the desired product. However, he was able to use some of the intermediates generated in new syntheses of cardenolides and cardanolides.

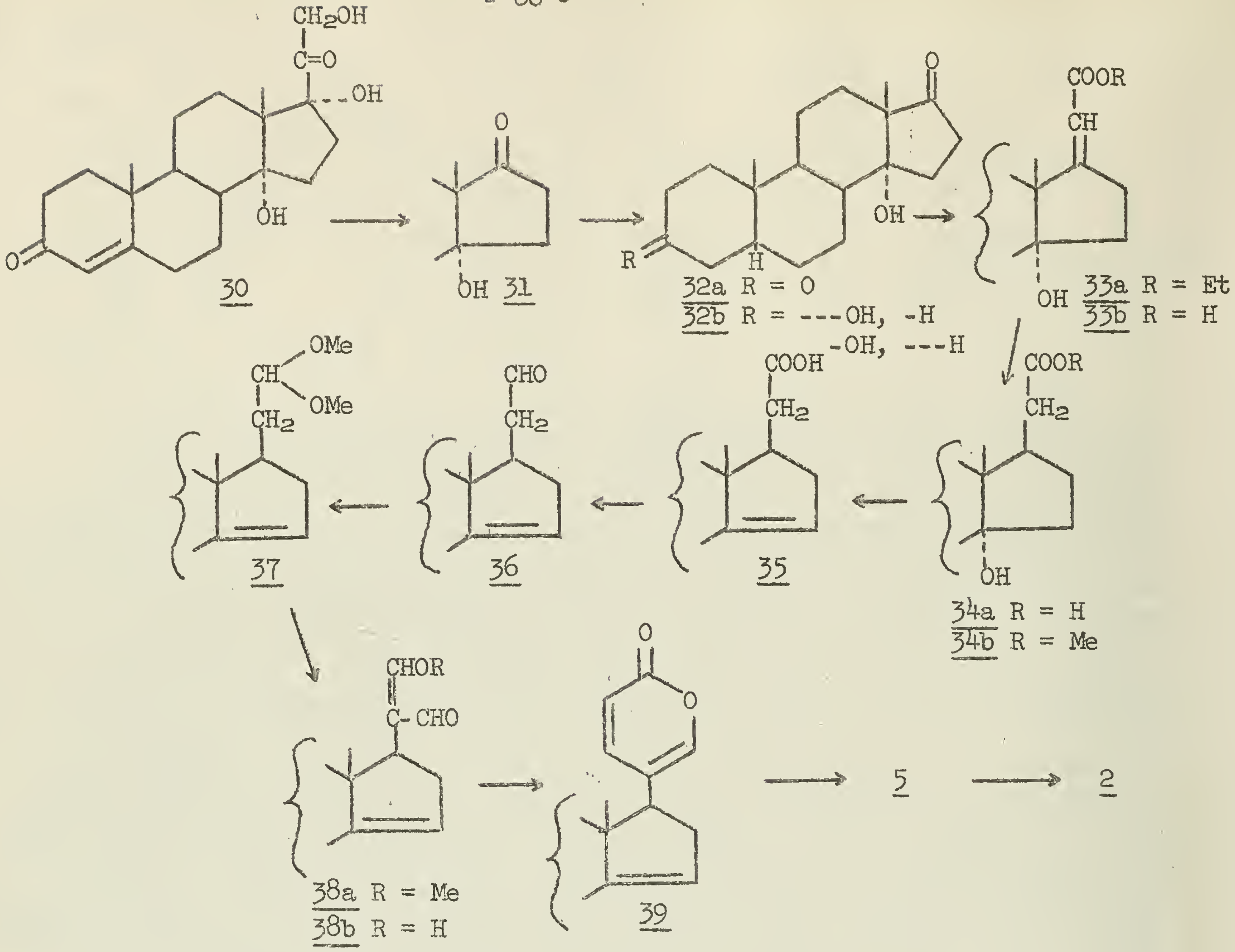
One successful synthesis is shown in the sequence 26 → 29, etc. Nitrile 26 was prepared by allowing dehydroepiandrosterone acetate to react with the carbanion derived from diethyl cyanomethylphosphonate. Compound 26 was then selectively reduced with $Pd/CaCO_3$ to yield saturated nitrile 27. Saponification of this product resulted in the corresponding acid, which was then converted to the acid chloride. Reduction of the chloride with $Pd/BaSO_4$ yielded aldehyde 28, which then condensed with piperidine, leading to an intermediate enamine. The crude enamine was alkylated with methyl acrylate in acetonitrile, giving a two-component mixture consisting of starting aldehyde and methyl ester 29. Conversion to enol lactone 20 was accomplished with p-toluenesulfonic acid in benzene. After considerable experimentation it was found that dehydrogenation could best be achieved by heating the enol lactone with sulfur at 221-227° to produce the desired bufadienolide.

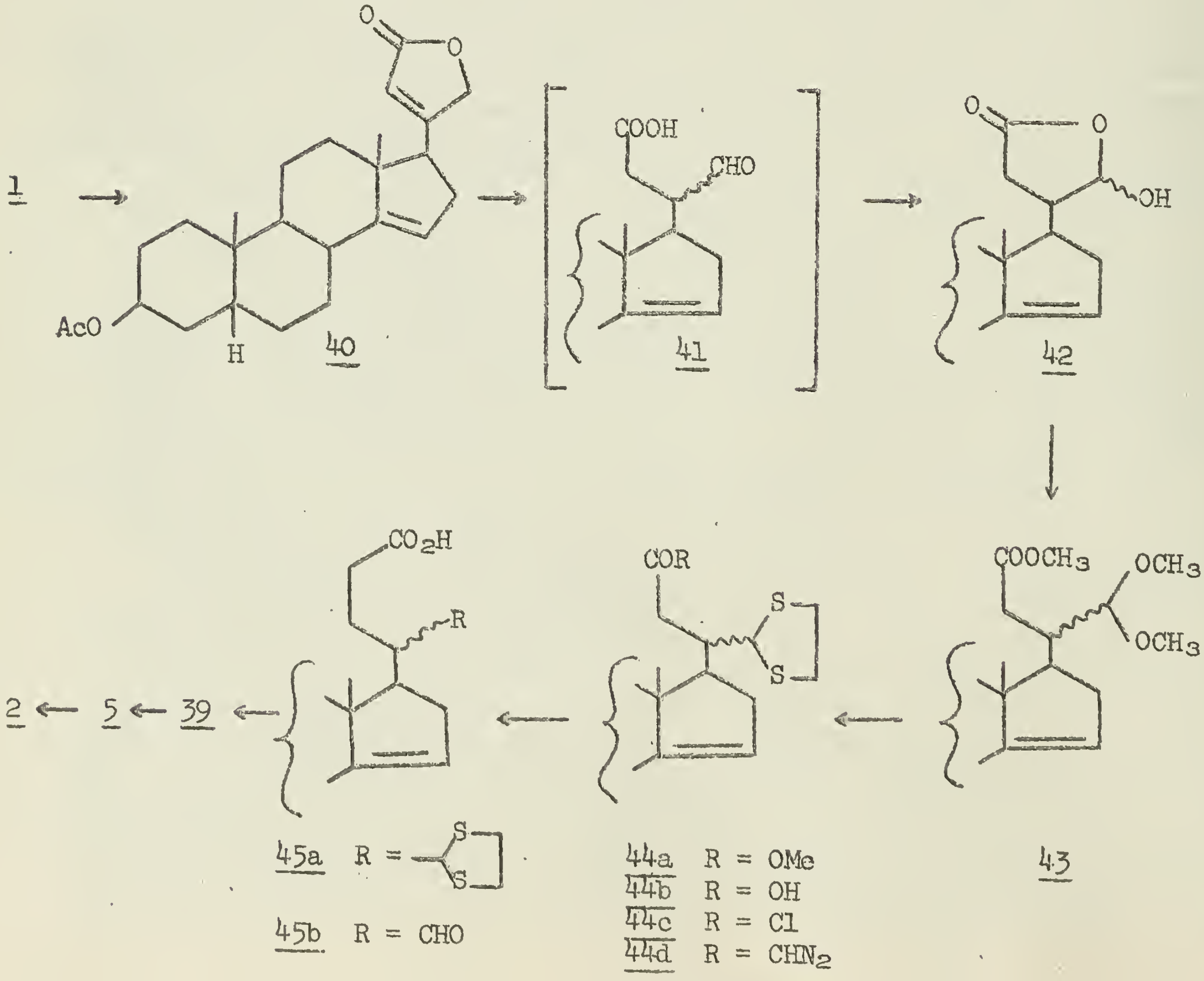




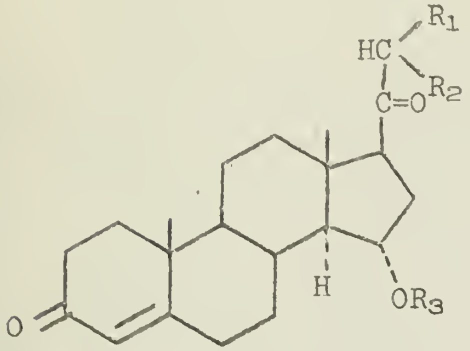
The years 1969-70 proved fruitful for the completion of syntheses of the naturally occuring bufadienolides. Sondheimer[33] reported the first synthesis of bufalin and resibufogenin by a pathway based on his previous bufadienolide synthesis: Starting with readily available 14α-hydroxycortexolone 30 and treating this with sodium bismuthate gave 31 in good yield. The steroid was then hydrogenated producing 32a, and the 3-keto group was selectively reduced with NaBH$_4$ in methanol to yield a mixture of the 3α- and 3β-ols 32b, which was then separated by chromatography on alumina. Utilizing only the α-epimer, presumably because it could be isolated in larger yield, and treating it with lithium ethoxyacetylide followed by rearrangement of the resulting intermediate with H$_2$SO$_4$, ethyl ester 33a was produced. The ester was then saponified to 33b. The $\Delta^{17(20)}$ linkage was then reduced with potassium in liquid ammonia. The saturated acid 34a was assigned the β configuration since it was expected that the thermodynamically more stable epimer would be formed. Methyl ester 34b was produced by reaction with diazomethane. After acetylating the 3-hydroxy group, 34b was dehydrated with POCl$_3$-pyridine to give the Δ^{14} olefin. Saponification led to the acid 35, which was reduced to the aldehyde 36 by reaction with excess N,N-carbonyldiimidazole followed by reduction with excess lithium tri-t-butoxyaluminum hydride. The acetal 37 was then prepared by reaction with methanol in the presence of p-toluenesulfonic acid. Treatment of the acetal with POCl$_3$-DMF yielded a mixture of the cis and trans isomers of 38, which was separated by preparative tlc to yield 60% of the cis isomer. This was then hydrolyzed with NaOH in aqueous ethanol to give the β-dialdehyde 38b. Ring closure was effected by means of a Reformatsky reaction using methyl bromoacetate. Preparative tlc resulted in the isolation of α-pyrone 39. At this point the 3α-acetate was saponified, converted to the p-toluenesulfonate and heated in DMF. The resulting 3β-formate was saponified to 3β-ol and reacetylated. The final stages of the synthesis required treatment of 39 with NBS in aqueous acetone and chromatography on basic alumina, resulting in the formation of the 3β-acetate of resibufogenin, presumably through an intermediate bromohydrin. The 3β-acetate was saponified to 5. Finally reduction of the epoxy group of 5 was accomplished with LiAlH$_4$, yielding synthetic bufalin 2.

Pettit[31] reported a somewhat simpler synthesis of bufalin from digitoxigenin, first prepared by Sondheimer.[34] Digitoxigenin was acetylated and dehydrated to 40. Lactol 42 was formed by treatment of 40 with sodium methoxide followed by acidification, possibly through intermediate 41. Methanolysis of the lactol with p-toluenesulfonic acid in methanol readily gave the ester acetal 43. The acetal was protected by forming an ethylene thioacetal with ethane dithiol/70% HClO$_4$. Methyl ester 44a was readily hydrolyzed, possibly due to neighboring group participation of the sulfur, to 44b. The acid chloride 44c was prepared followed by conversion to diazoketone 44d and subsequent formation of carboxylic acid 45a using Ag$_2$O. The removal of the thioacetal was accomplished with a mixture of HgO/HgCl$_2$/HOAc to yield 45b. Cyclization was accomplished using p-toluenesulfonic acid as a catalyst, and dehydrogenation with sulfur resulted in dehydrobufalin 39. The Δ^{14} olefin was epoxidized with m-chloroperbenzoic acid, which was ring opened to bufalin with[24] LiAlH$_4$.

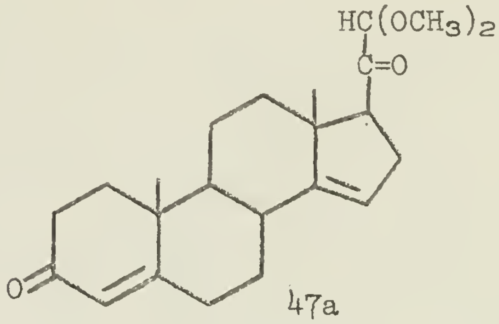

30
31
32a R = O
32b R = ---OH, -H
-OH, ---H
33a R = Et
33b R = H
34a R = H
34b R = Me
35
36
37
38a R = Me
38b R = H
39
5
2


1
40
41
42
43
44a R = OMe
44b R = OH
44c R = Cl
44d R = CHN2
45a R =
45b R = CHO
39
5
2

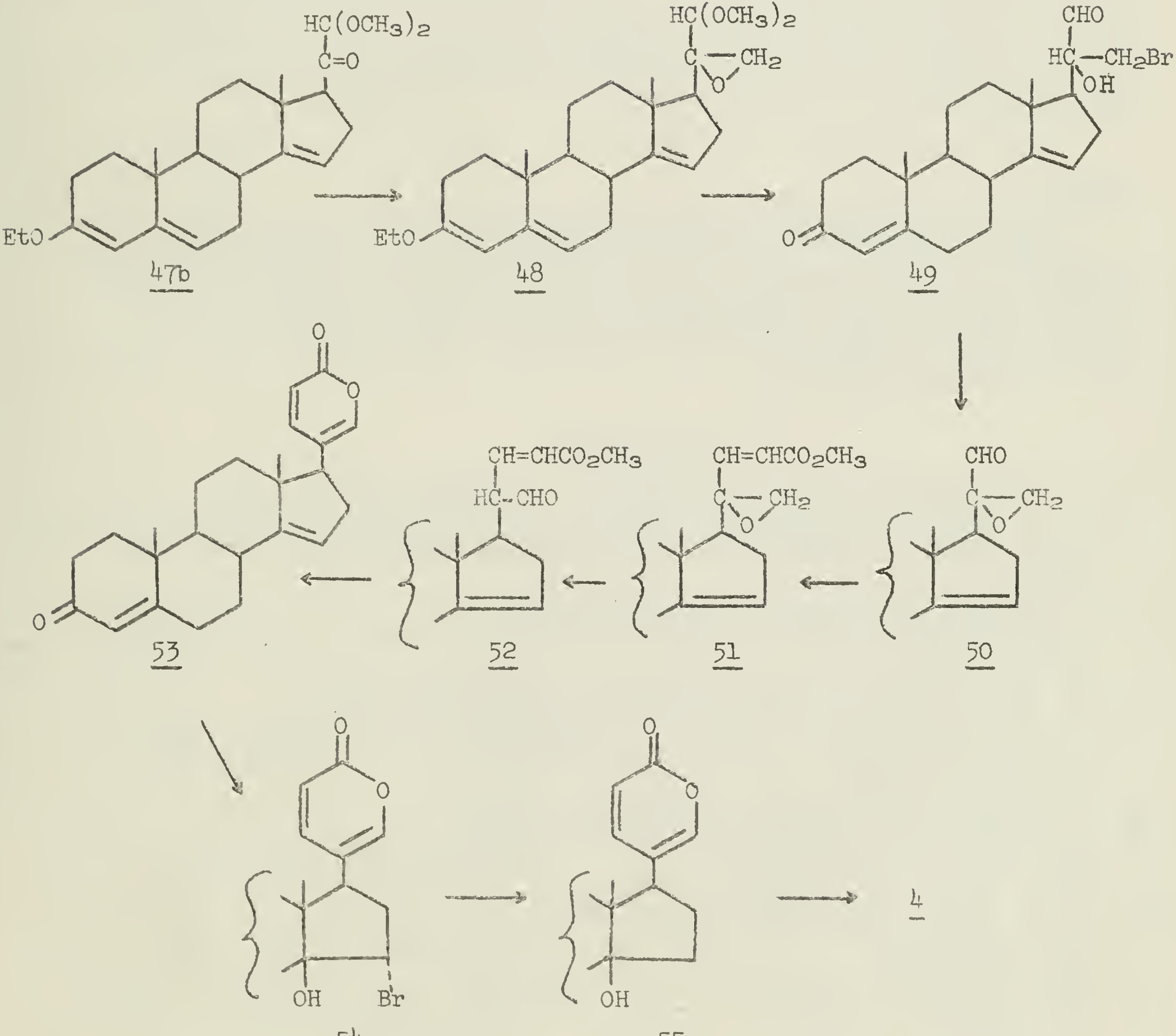
German workers have recently reported the first successful synthesis of scillaren. The partial oxidation of readily available 15α-hydroxycor-



46a $R_1 = R_3 = H$; $R_2 = OH$
46b $R_1 = R_2 = OH$; $R_3 = H$
46c $R_1 = R_2 = OCH_3$; $R_3 = H$
46d $R_1 = R_2 = OCH_3$; $R_3 = Ts$



47a



texenone 46a with cupric acetate in aqueous methanol resulted in hydrated aldehyde 46b which was then converted to acetal 46c with methanolic HCl. The 15α-hydroxy group was converted to the tosylate 46d, which underwent elimination with Li_2CO_3 in DMF to 47a. A new α-pyrone synthesis had to be devised to preserve the unsaturated scillaren ring system. Consequently, the 4-ene-3-one grouping was protected using triethyl orthoformate/H^+ in dioxane which resulted in 47b. Treating this intermediate with dimethylsulfonium methylid yielded the epoxide 48. The epoxide was opened with aqueous HBr which also removed the protecting group at the 3-position and converted the acetal to the aldehyde, leading to bromohydrin 49. The epoxide was regenerated with triethylamine in THF yielding 50. The aldehyde group was then selectively attacked with sodium (carbomethoxymethyl)diethylphosphonate to produce 51. The epoxide was converted back to the aldehydic group with etheral boron trifluoride. Nmr showed neither isomerization of the Δ^{14}-double bond resulting from this procedure nor any interference from the 4-ene-3-one system. Lactonization was accomplished in HCl/MeOH and yielded 53 also without any isomerization. Utilizing N,N-dibromobenzenesulfonamide in aqueous dioxane resulted in 15α-, 14β-bromohydrin 54. Hydrogenolysis removed the 15α-bromine to produce scillarenone 55. Finally, the 3-keto group was reduced with lithium tri-t-butoxyaluminum hydride in THF yielding synthetic scillaren 4, which was compared directly with the naturally occurring material.

SUMMARY

Application of some new and some previously known procedures has resulted in the total synthesis of some members of the bufadienolide family of steroids. Prior to 1969 no member of this classic category of steroids had been synthesized. Following the discovery that some bufadienolides possess antitumor properties, the preparation of new members of this series is of continuing interest.

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RECENT STUDIES OF AROMATIC CHARGE TRANSFER COMPLEXES

Reported by E. Perozzi December 3, 1970

INTRODUCTION

Recently there has been much interest in a class of compounds known as charge transfer complexes.[1,2] These complexes are known to exhibit biological activity,[3] to occur during chemical reactions,[4] and to possess electrical conductivity properties.[5] This seminar will cover recent work on the physical and biological properties of these complexes.

THEORETICAL

Charge transfer complexes are formed between electron-rich molecules called donors (D) and electron deficient molecules called acceptors (A). There are three main types[6] designated as π-σ, n-σ, or π-π complexes in which the first symbol refers to the donor and the second to the acceptor. Thus, in a π-σ complex a π-bond of the donor contributes its electrons to a σ-bond of an acceptor as in the benzene-bromine complex.[7] An energy level diagram[8] shows the charge transfer (CT) transition to occur from the filled bonding molecular orbitals of the donor to the unfilled antibonding MO's of the acceptor (Figure 1). Also note that I, the ionization potential, is the energy needed to remove an electron from the highest filled level of the donor to infinity, and EA, the electron affinity, is the energy gained when an electron is taken from infinity to the lowest unfilled antibonding MO. If I > EA then energy must be invested to transfer the electron; whereas, if EA > I, energy would be gained and and the electron would transfer spontaneously.[3] The total energy of the system, E, is equal to I-EA.

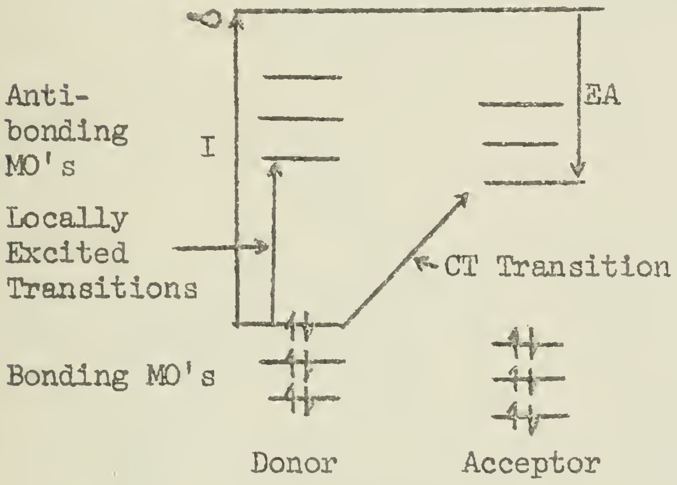


Figure 1

ELECTRONIC SPECTRA

One evidence of formation of a charge transfer complex is given by its electronic spectrum. A new band appears when solutions of the donor and acceptor are mixed together. The resulting resonance structures may be written $(D\ldots A \leftrightarrow D^{+}\ldots A^{-}) \xrightarrow{h\nu_{CT}} (D^{+}\ldots A^{-} \leftrightarrow D\ldots A)$ for a CT complex.[9,31]

A series of measurements were made on a group of alkoxy benzene donors (ROPh) with tetracyanoethylene (TCNE) as acceptor.[10] Table 1 shows two charge transfer transitions, CT1 and CT2, their extinction coefficients, ϵ_c, the association constants, K_c, the uv spectra for the uncomplexed donors, and two donor ionization potentials. The equilibrium constant is derived[7] from the Beer Lambert law: $\log I_0/I = D = \epsilon[C]l$ where D is the optical density, ϵ is the extinction coefficient, l is the cell thickness, and [C] is the concentration of the complex. The equilibrium $B + A \overset{K}{\rightleftharpoons} C$ may be written with initial concentrations of [B], [A], and 0 and final concentrations of [B-C], [A-C], and [C] respectively. If [B] >> [A], then $[B\text{-}C] \simeq [B]$ and $K = [C]/[B][A\text{-}C]$. Now substituting the Beer Lambert equations into this equation and rearranging gives:

$$\frac{1}{D} = \frac{1}{K[A]l\epsilon[B]} + \frac{1}{[A]l\epsilon}$$

A graph of $1/D$ vs $1/[B]$ gives a straight line from which intercept/slope = $K[A]l\varepsilon/[A]l\varepsilon = K$.

In Table 1 there are two charge transfer transitions. This may be understood if one examines the degenerate highest filled molecular π-orbitals of benzene $\Psi(E_{1_a})$ and $\Psi(E_{1_b})$ which are linear combinations of the atomic p-orbitals (ϕ_0-ϕ_5) as shown:[11]

$$\Psi(E_{1_a}) = 1/\sqrt{12}\,(2\phi_0 + \phi_1 - \phi_2 - 2\phi_3 - \phi_4 + \phi_5)$$
$$\Psi(E_{1_b}) = 1/2\,(\phi_1 + \phi_2 - \phi_4 - \phi_5)$$

Note that $\Psi(E_{1_a})$ uses all of the atomic p-orbitals of the ring whereas $\Psi(E_{1_b})$ does not use ϕ_0 and ϕ_3. Thus substitution at ϕ_0 (the 1-position on the benzene ring) leaves $\Psi(E_{1_b})$ unaffected but changes the energy of $\Psi(E_{1_a})$ resulting in the two charge transfer bands. This also explains why one band is dependent on substituents and the other is not. The substituent dependence of the second CT band on wavelength varies as Me > Et > i-Pr << t-Bu.[10] This may be rationalized if resonance is considered since there must be a coplanar alignment of the oxygen lone pair electrons and the aromatic π-electrons. Presumably, the t-butyl group sterically inhibits this resonance.

The number of molecules in a charge transfer complex may be determined from a Job plot.[12] Plotting absorbance at the charge transfer transition vs mole percent of donor and keeping the molarity constant by adding a sufficient amount of acceptor gives a symmetric curve for 1:1 complexes. In the case of 1,4-dimethoxybenzene as donor and N-methyl-4-cyanopyridinium chloride as acceptor,[13] the plot illustrated in Figure 2 is obtained. The different wavelengths correspond to different portions of the CT band. The curve is symmetric about 50% donor and therefore indicates a 1:1 complex. Complexes may crystallize in other than 1:1 ratios,[14] and when a phenanthrene-s-trinitrobenzene 1:1 complex was recrystallized from solutions containing 1:1 anthracene-s-trinitrobenzene, a series of crystals was obtained varying in color from yellow to orange.[15] These were assumed to be anthracene/phenanthrene-s-trinitrobenzene complexes.

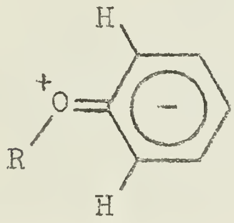


Illustration of
Alkoxy Benzene Resonance

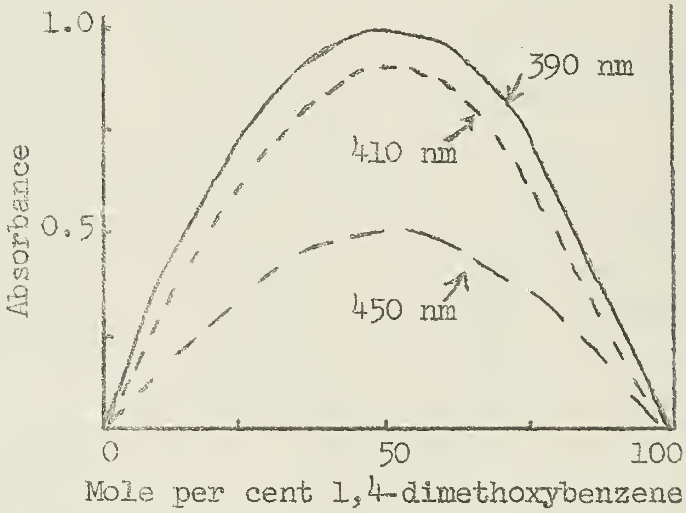


Figure 2

The observed color of a number of weak (or contact) charge transfer complexes disappears when in the solid phase.[16] Examination of Table 2 shows the first three complexes to have small association constants and the last three to have relatively large ones.

Phase diagrams showed the first three solids to be simple eutectic mixtures in which the solids can exist in two phases. This causes a relatively small number of donor and acceptor molecules to be in contact at the crystal interfaces. In the last three cases, the mutual attraction of donor and acceptor must overcome the tendency of identical molecules to combine in the same crystal.[16]

Table 1

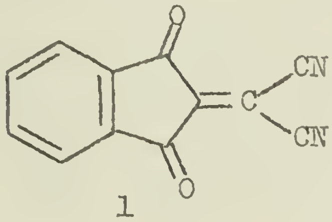
[ROPh] = 0.1-1.0 M, [TCNE] = 2 x 10^{-3} M, Solvent = CH_2Cl_2

	λ_{max} (nm)		ϵ_c (l. $mole^{-1}$ cm^{-1})		K_c (l. $mole^{-1}$)		uv	Ioniz.
	CT1	CT2	CT1	CT2	CT1	CT2	spectra	potential
$ClCH_2CH_2$	384	492	1000	1250	0.33	0.24	--	--
Me	385	505	1430	2220	0.35	0.27	271	9.37,8.54
Et	387	513	1540	1540	0.37	0.48	271	--
i-Pr	391	522	1330	2000	0.35	0.26	273	--
t-Bu	390	462	1600	1300	0.4	0.4	270	9.33,8.75

Table 2

Donor	Acceptor	Solvent	K (l. $mole^{-1}$)	Sol'n or melt color	Color of solid
Diphenylamine	p-chloronitrobenzene	C_6H_{12}	.32	Orange	White
Triphenylamine	p-dinitrobenzene	CH_2Cl_2	.21	Red	White
"	p-chloranil	CH_2Cl_2	.16	Blue-green	Pale cream
Anthracene	s-trinitrobenzene	CH_2Cl_2	2.61	Orange-red	Orange
N,N-Dimethylaniline	"	CH_2Cl_2	.75	Red	Magenta
Durene	TCNE	CH_2Cl_2	3.31	Magenta	Magenta

When ionization potential measurements for the donor are available, a linear relationship between the ionization potential, I, and the energy of the charge transfer may be demonstrated. For example, in the case of 2-dicyanomethyleneindane-1,3-dione (1) and various donor molecules, the energy of the charge transfer band was plotted[17a] against the ionization potentials of the donors, and a straight line having the equation $h\nu_{CT} = 0.95 I_D - 4.77$ resulted in which the constants are in units of electron volts.

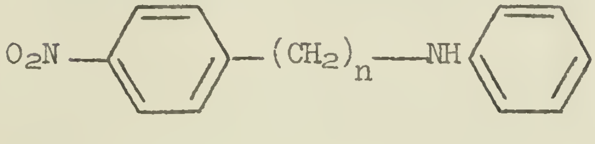


1

The solvent has been shown to affect the position of the charge transfer band in the pyridine-iodine case[17b] and the shift was shown to correlate with the solubility parameter of the solvent. A red gas-to-solution shift has also been observed[17c,d] when comparing vapor phase measurements of the charge transfer complexes with solution measurements.

INTRAMOLECULAR CHARGE TRANSFER COMPLEXES

Compounds of the following general type have been prepared[18] in which n = 1,2,3,4,5,7. In compounds having n equal to 1 through 3, subtraction of the absorption curve of n = 7 from the smaller n-compounds gives the result in Table 3.

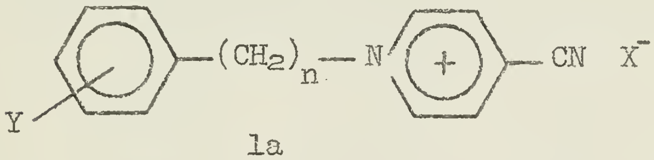


(In n = 7 there is assumed to be no CT interaction.) Thus, an intramolecular charge transfer occurs when the portions of the molecule are sterically near each other. Running the spectra in acetic acid causes the CT band in the n = 3 case to disappear presumably because strong hydrogen bonding with the nitrogen atom decreases the complex forming power of the donor group.[18]

Table 3. Solvent: 95% EtOH

n	1	2	3	4&5
λ_{max}	345-55 (nm)	335	ca. 330	---
ϵ_{max}	270	980	(shoulder)	---

In another case compounds of type 1a were prepared.[19] The workers[20] were able to relate the energy of the CT transition linearly to the ionization potential of the donor giving for water as solvent: $h\nu = 0.83I_D - 3.00$ and for 96% EtOH: $h\nu = 0.85I_D - 3.27$. It was postulated that for the case of n equal to 1 there would be overlap between the C_1 p-orbital of the donor and the ring nitrogen p-orbital of the acceptor. (Figure 4). This is interesting since the intensity of the CT band is the same order of magnitude as the N-methylcyanopyridinium ion and methoxybenzene complex.[13] In this two molecule complex the components are assumed to stack in parallel planes. In the above case this is of course impossible.



1a

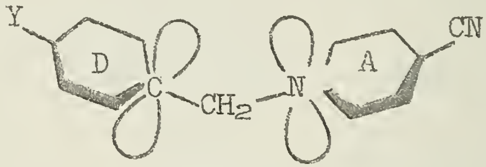


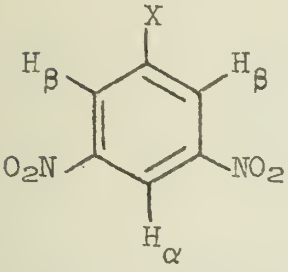
Figure 4

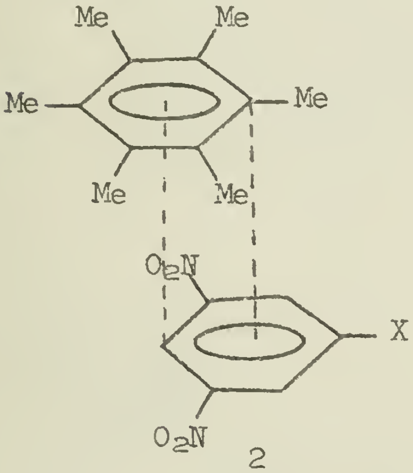
NMR SPECTRA

When charge transfer complexes form, the chemical shifts of the protons change since they are in different environments. Foster and Fyfe[21a] derived an expression $\Delta/[D] = -\Delta K + \Delta_0 K$ where $\Delta = \delta^A_{obs} - \delta^A_0$ and $\Delta_0 = \delta^A_{AD} - \delta^A_0$ for the case of a large excess of donor. In this equation K is the association constant, δ^A_{obs} is the observed shift of the acceptor protons in the uncomplexed state, and δ^A_{AD} is the shift of the acceptor protons in the pure complex.

An nmr study was made on complexes of hexamethylbenzene and 1-substituted 3,5-dinitrobenzenes.[22] The results are tabulated in Table 4. A reasonably linear correlation was obtained between $\log_{10}K_c$ and the Hammett σ_{meta} for these groups. Foreman and Foster assumed that the most perturbed protons have the largest Δ_0 value and lie closest to the center of the two-component complex.[21b] Thus orientations 2 or 3 may account for the observed differences. In another set of nmr measurements, Emslie et al.[22] studied mono-n-alkylbenzenes with fluoranil, s-trinitrobenzene (s-TNB), and TCNE. The number of carbon atoms vs the association constant was plotted and a saw-tooth pattern was observed (Figure 5). In the case of fluoranil as an acceptor, the most pronounced variation was observed. Even-numbered chains had the higher association constants and odd-numbered ones had the lower ones. In the case of s-TNB as acceptor, the trend was reversed although it was less pronounced. This may be due to steric packing requirements,[21c] although the published work has not yet appeared.

Table 4

T = 33.5°C	X	K_c (Kg. solvent/mole)		Δ_o(Hz)	
		H_α	H_β	H_α	H_β
 X H_β H_β O_2N NO_2 H_α	NMe_2	1.0	0.9	40	38
	OMe	1.1	1.7	61	48
	CF_3	1.5	1.6	94	50
	CN	3.3	3.5	75	69
	NO_2	5.3		65	
	H	1.0	1.0	71	72



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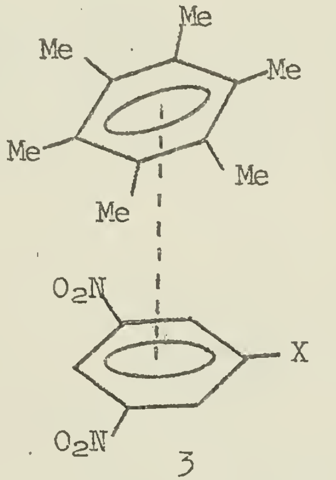

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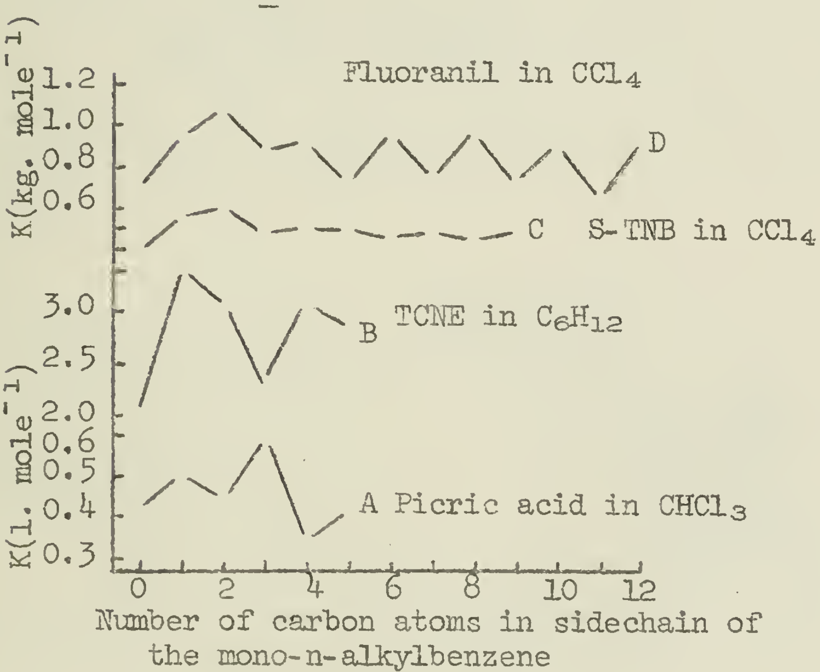
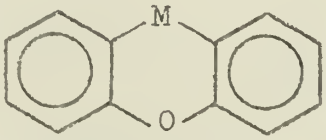
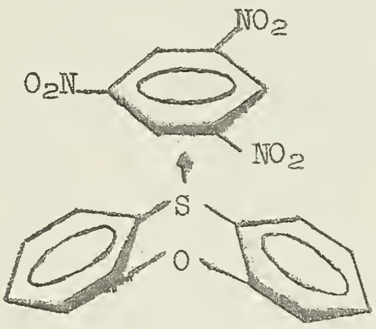


Figure 5 (Ref. 21)

STEREOCHEMISTRY

Complexes of the general form:  with s-TNB as an acceptor were prepared[9,23] having M = O, S, Se, and Te. The electronegativities of these elements are 3.50, 2.44, 2.48, and 2.01, respectively. The association constants in all four cases were similar. To explain the effect of the considerable increase in electronegativity in passing from sulfur to oxygen, it was assumed that the donor center is located on the S, Se, or Te whereas in the oxygen case it was located over the benzene ring. To test this hypothesis electronic spectral data were obtained.[23] A spectrum of diethyl sulfide and *s*-TNB gave a CT band in the same region of the spectrum (416 nm) as phenoxathiine-*s*-TNB (420 nm) (*4*). However a spectrum of diethyl ether with *s*-TNB was transparent in this region, indicating that a complex could not form. The dibenzo-*p*-dioxin-*s*-TNB complex (*5*) had a CT band at 417 nm. Also diphenyl ether with *s*-TNB gave a CT band at 417 nm. Figure 6 shows the expected sandwich structure for a crystal of *5*.

Stereochemical considerations are also involved in certain chemical reactions. In the case of maleic anhydride and anthracene, SCF-MO calculations were done.[24] These showed that in the ground state the maleic anhydride molecule is centered over one of the outer benzene rings whereas in the lowest charge transfer state, the maleic anhydride is over the middle of the anthracene molecule. It may then be considered that the charge transfer interaction takes part in the Diels-Alder reaction which occurs between maleic anhydride and anthracene at the 9,10 positions of anthracene.[24]



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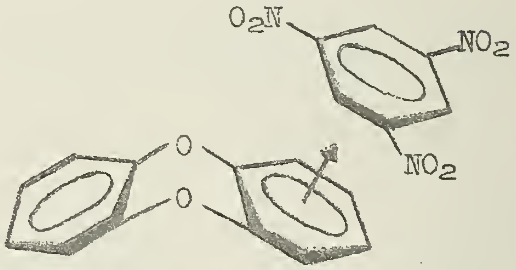

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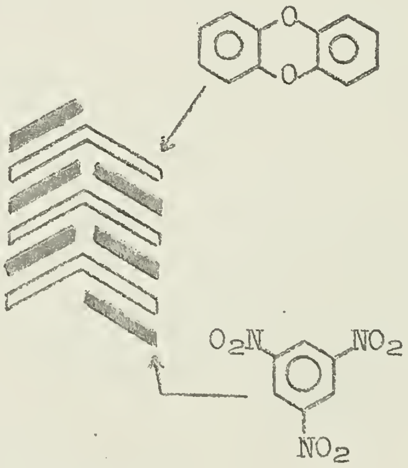

Figure 6

ELECTRICAL SEMICONDUCTIVITY

Band theory may be used to understand the electrical properties of charge transfer complexes.[3,50] This states that the energy levels of an atom are split when coupled electronically to another atom. When many such atoms are placed in close proximity, as in a crystal, the levels are split many times and are very close in energy with the result that thermal excitation suffices to cause them to merge and appear as one continuous band. For our purposes we many think of only the filled valence band and a higher energy unfilled conduction band separated by an energy gap. For intrinsic conductivity, the thermal generation of carriers requires that this energy gap, E_G, be given[25,26] by $E_G = I_C - A_C$ where I_C and A_C are the energies of removing and adding an electron to the crystal. I_C can also be related to the molecular ionization energy, I_G, by the polarization energy, P, which is the energy released when a charged molecule is placed in an environment of neutral molecules which then become polarized. Thus $I_C = I_G - P$. A_C can also be related to the molecular property A_G by the equation: $A_C = A_G + P$. Thus we may write $E_G = I_G - A_G - 2P$ by combining the above equations. Values of I_C have been obtained for the charge transfer complexes s-TNB-coronene (5.62 ev), s-TNB-perylene (5.52 ev), and quinolinium-tetracyanoquinodimethane (4.85 ev).[27] These are obtained by placing some of the substance sublimed onto an electrode in the center of an evacuated graphite sphere. A beam of uv light is then focused on the sample which is connected to an external battery and electrometer circuit. The electrical output is then measured as a function of the wavelength of light. The I_C value is taken where the threshold energy occurs (or that energy where conductivity just appears).

The observed activation energy, E_A, is the energy necessary to populate the excited state so that conduction can occur.[5a] It arises experimentally from a measurement of electrical conductivity as a function of temperature. The values may be related by the expression $\sigma = \sigma_0 \exp(-E_{act}/kT)$ where σ is the observed conductivity, σ_0 is a constant, and T is the temperature. The value of E_{act} is equal to $E_G/2$ in which E_G is the above-mentioned energy gap. The factor of 1/2 arises since it is possible to distribute electrons in the conduction band independently from an equal number of holes in the valence band.[5a]

By restating the above equation for σ, we may obtain $\log \sigma = -E_{act}/kT + \log \sigma_0$. Thus a plot of log σ vs 1/T should be linear and the slope is equal to the activation energy. Table 5 shows some conductivities at 30° ($\sigma_{30°}$), activation energies, and compositions for various charge transfer complexes.[14]

Table 5

System	Composition	$\sigma_{30°}$ (Ω^{-1} cm^{-1})	E_{act} (ev)
p-phenylenediamine-I_2	0.8:1	2.5×10^{-9}	0.38
"	1:1	2.6×10^{-9}	0.28
benzidine-I_2	0.75:1	8.1×10^{-6}	0.28
phenothiazine-I_2	1:3	9.2×10^{-5}	0.43

For organic semiconductors in general, two mechanisms have been proposed to account for the movement of charge in an organic solid.[28] One theory proposes an excitation of an electron to an upper level of a molecule followed by tunneling of the positive hole and of the negative charge (cf. Figures 7a and 7b).

The second theory called the orbital overlap theory proposes biradical formation under the influence of the field and the temperature. An electrode then abstracts an electron and the hole thus formed then moves by "electron hopping" (cf. Figure 8).[28] Both mechanisms seem to hold in various instances,[28] so further work should be done to try to determine the operable mechanisms.

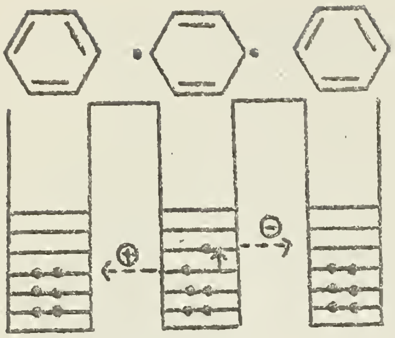

Figure 7a

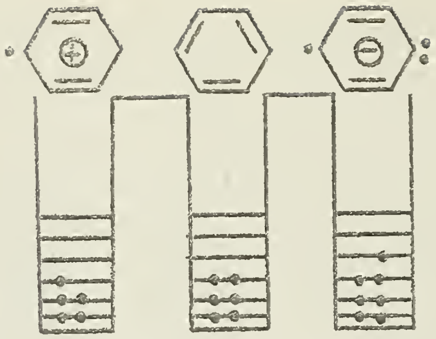

Figure 7b

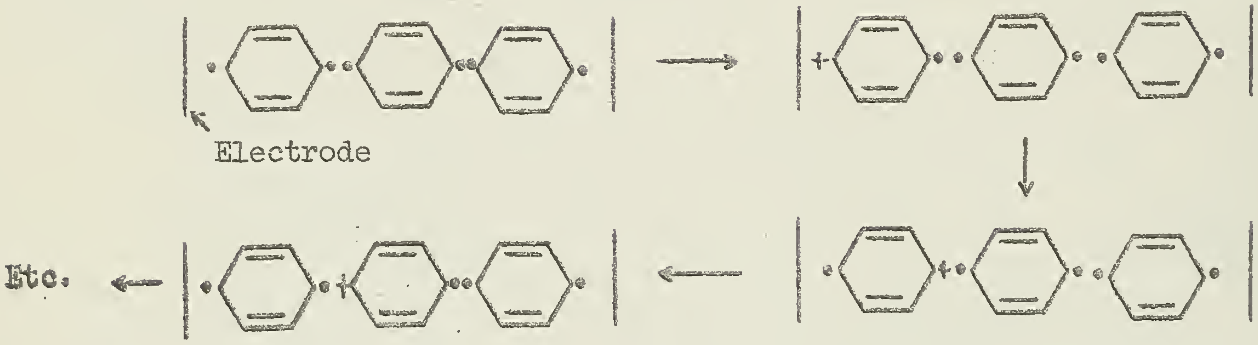

Figure 8

BIOLOGICAL APPLICATIONS

Paraquat or N,N'-dimethyl-4,4'-bipyridylium dichloride is a general spectrum non-residual herbicide. It is thought to exert its effect upon photosynthesis by a charge transfer mechanism and indeed it was shown[29] to be a good electron acceptor when paired with such donors as pyrene (3.4), hydroquinone (5.2), and p-aminophenol (7.7). The numbers in parentheses are association constants expressed in l. mole^{-1}.

One of the most interesting possibilities is that charge transfer complexes are linked to cancer.[3] A study was made on 4-nitroquinoline-1-oxide, a potent carcinogen.[30] The compound 4-nitropyridine-1-oxide, however, lacks biological activity. Charge transfer spectra were obtained for the quinoline case but not for the pyridine compound. The same ability to form charge transfer complexes was found[30] for the metabolites of the quinoline compound (4-hydroxylaminoquinoline-1-oxide) compared to the pyridine compound (4-hydroxylaminopyridine-1-oxide). Thus, a connection may be made between the cancer producing agents and their ability to form charge transfer complexes.

CONCLUSIONS

Organic charge transfer complexes should prove to be a fruitful area of research in the future. The study of these complexes shows that they are good electrical semiconductors and that in certain instances charge transfer complex formation may be linked to cancer and other biological phenomena.

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DIKETOPIPERAZINE-DERIVED MOLD METABOLITES

Reported by R. L. Cundall December 7, 1970

2,5-Diketopiperazines (DKP's) or 2,5-piperazinediones bear a close relationship to amino acids as anhydrides of dipeptides, and are often referred to as anhydrides. In glycine anhydride (c-gly-gly), the parent DKP, the ring has been shown by X-ray analysis to be nearly planar.[1] 3,6-Disubstituted-DKP's can exist in three optical forms, two optically active cis forms (c-L-L)(c-D-D) and an inactive trans form (c-L-D). The principle synthetic procedures for simple DKP derivatives were developed prior to 1910 by German chemists and are described in detail by Greenstein[2] and Platt.[3] The heating of an amino acid in a stream of CO_2[4] or HCl gas,[5] or in polyhydroxy solvents,[6] or of an amino acid ester in a variety of solvents,[7,8] has yielded the dimeric, anhydride DKP's. Some amino acid lactones dimerize at room temperature.[9] Dipeptide esters[10] and α-haloacylaminoacid esters[11] deposit DKP's on standing in methanolic ammonia. Many dipeptides exhibit high intermolecular condensation tendencies, cyclizing in water or dilute hydrochloric acid at moderate temperatures,[12] and dipeptides containing proline form DKP's almost spontaneously.[13]

Recent techniques directed toward the synthesis of optically pure DKP's include heating the unprotected dipeptide in phenol,[14] cyclization of dipeptide methyl ester formates,[15] and hydrogenolysis of benzyloxycarbonyl dipeptide methyl esters.[16] However, Slater[17] in 1969 found that the methanolic ammonia method of Fischer[10] still provides very satisfactory results.

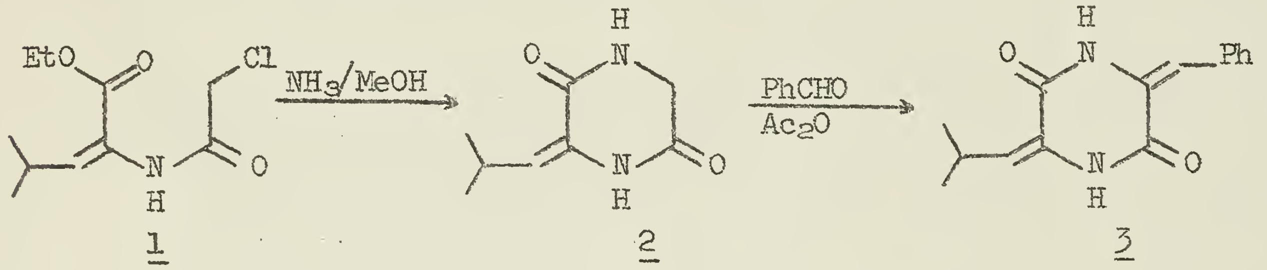
Isolation of DKP's in protein hydrolysates has been reported as the isolation of natural products. It is likely, however, that many isolated simple DKP's are the result of anhydride formation during extraction procedures. Mitscher, et al.[18] have restated a warning for careful control experiments before presentation of any DKP as a natural product. Nevertheless, authentic DKP derived products have been reported.

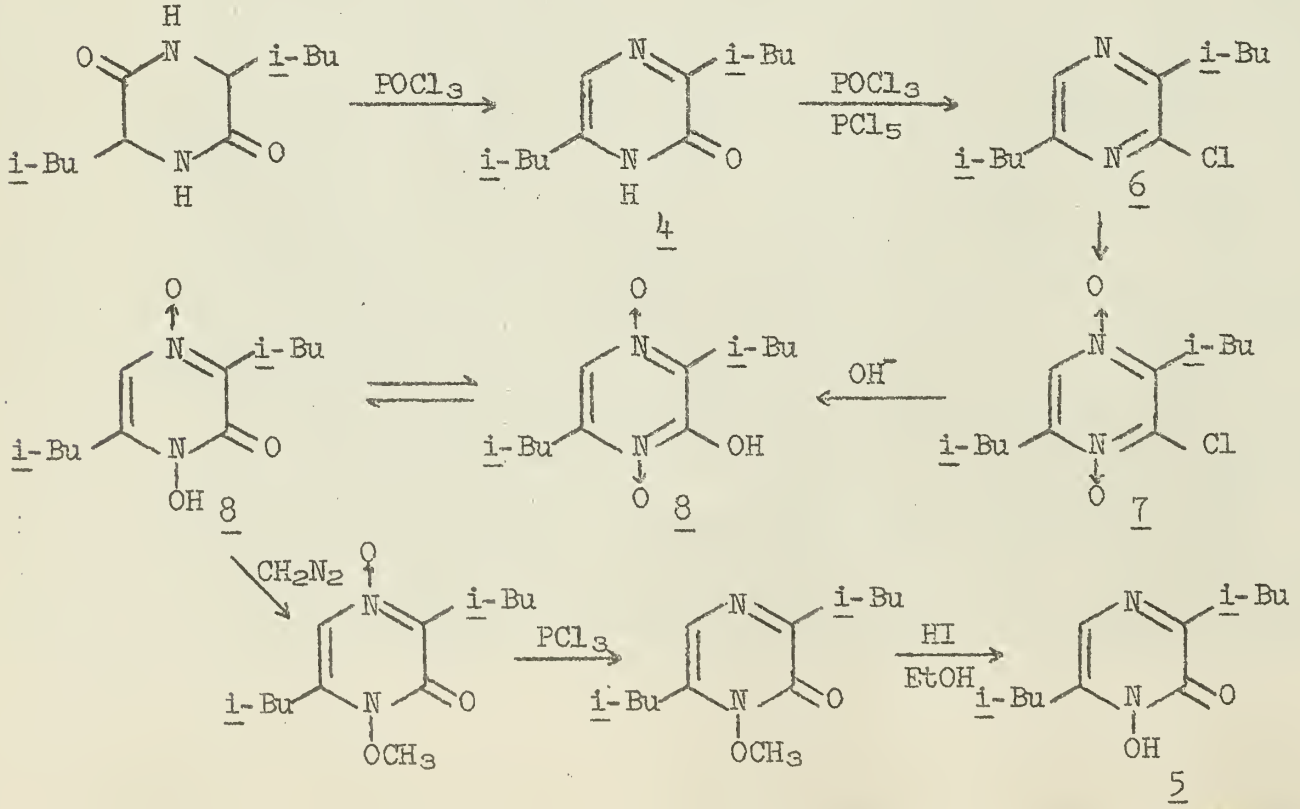
Khoklov and Lokshin extracted an antifungal antibiotic principle from Streptomyces albus and S. noursei and called it albonoursin.[19] Alkaline hydrolysis of albonoursin yielded benzaldehyde, isobutyraldehyde and ammonia; acid hydrolysis yielded phenylpyruvic acid, isovaleroylformic acid and two moles of ammonia. These facts, together with mass spectral and ir data, showed the compound to be 6-benzylidine-3-isobutylidine-DKP (3). The dibenzylidine-DKP was also isolated. Others have isolated the corresponding dihydro derivatives and L-leucylphenylalanine anhydride (c-L-leu-L-phe)[20] and c-L-phe-L-phe[21] from S. noursei. The dibenzylidine-DKP has also been isolated from Nocardaceae[22] and from S. thioluteus.[23] Gerber isolated 3-anisylidine-6-benzylidine-DKP and substantiated the report by separation of the compound from the product mixture of glycine anhydride, p-anisaldehyde, benzaldehyde and sodium acetate in acetic anhydride,[23] applying the active-methylene condensation method of Sasaki.[24] The synthesis of albonoursin, reported in 1969, involved benzaldehyde condensation with 3-isobutylidine-DKP (2) formed by cyclization in methanolic ammonia of the ethyl ester of the dipeptide precursor, ethyl 2-(2-chloroacetamido)-4-methyl-2-pentenoate (1).[25] L-Phenylalanine and L-leucine have been demonstrated as biosynthetic precursors of albonoursin and L-phenylalanine, of the dibenzylidine-DKP.[25]

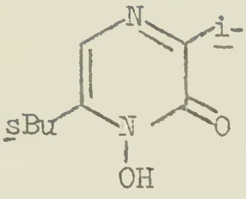
Flavocal and aspergillic acid, a bactericidal antibiotic, isolates from Aspergillus flavus reviewed by Pratt,[3] and pulcherrimic acid, an iron complexing pigment of Candida pulcherrima,[27] are biosynthetically related to DKP's. Several compounds similar to aspergillic acid and flavocol which are named as aspergillic acid derivatives have also been isolated from Aspergillus species.[28] The active moiety of aspergillic acid and related compounds was determined by comparison of structure to toxicity in the mouse.[29] The fluorscence characteristics of these compounds correspond directly to their toxicity and depend on N-hydroxy-oxide substitution.

Ohta has synthesized flavacol, neo-,[30] deoxy- and DL-aspergillic acids[31] and pulcherrimic acid[32] from DKP's. Flavocol (4) and neoaspergillic acid (5) were produced by heating DL-leucine anhydride (c-DL-leu-leu) with phosphorus oxychloride. Flavacol was quantitatively converted to 6 by heating with phosphorus oxy- and pentachlorides. The dioxide 7 was formed by treatment of 6 with permaleic acid, and chloride was displaced with ethanolic potassium hydroxide to yield 2-hydroxy-3,6-diisobutylpyrazine-1,4-dioxide (8). Methylation with diazomethane, reduction with phosphorus trichloride and demethylation with hydroiodic acid-ethanol yielded neoaspergillic acid (5). In much the same manner c-DL-leu-ile was converted to aspergillic (10) and deoxyaspergillic acids (11). Pulcherrimic acid was obtained from leucine anhydride by reaction with phosphorus oxychloride to form the symmetrical dichloride 12; treatment of 12 with permaleic acid to give 2,5-dichloro-3,6-diisobutylpyrazin-1,4-dioxide. Treatment with sodium methoxide, hydrolysis with hydrochloric acid, and reaction with ferric chloride gave the pigment pulcherrimin. Pulcherrimin on successive treatment with dilute acid and base gave the chelate, pulcherrimic acid (13).

Cook and Slater had postulated the structure of pulcherrimic acid as dihydroxy-L-leucine anhydride,[27] but proved themselves mistaken by synthesis of the postulated acid.[33] MacDonald[34] on the basis of nmr data, which exhibited no ring hydrogens, and zinc-acetic acid reduction, which yielded optically inactive DL-leucine anhydride, postulated the structure 13 substantiated by Ohta's synthesis. MacDonald has also shown the acid to be biosyntheticly derived from L-leucine and has trapped the intermediate L-leucine anhydride.[35]







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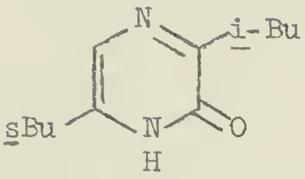

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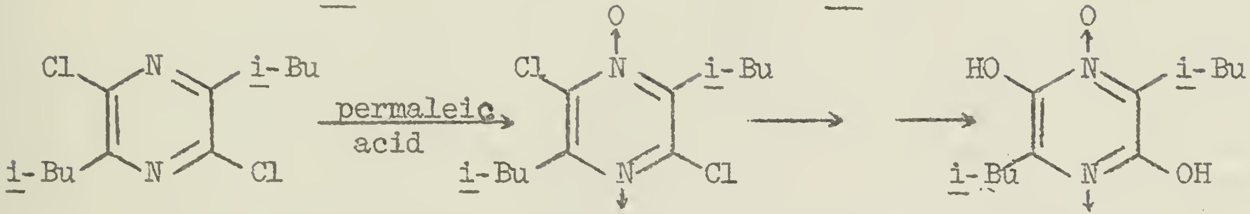

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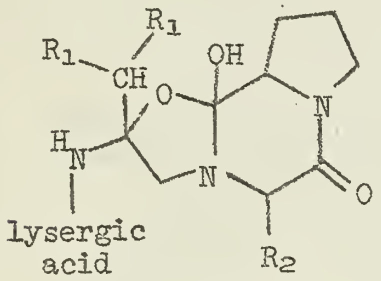
The ergot alkaloids, ancient medicinal agents which are derivatives of lysergic acid, incorporate a number of compounds with DKP-derived peptide portions 14. The subject has been covered by Stoll.[36] Other compounds which incorporate a readily recognizable cyclic dipeptide structure include echinulin, an extract from the mycelium of several Aspergillus molds, and mycelianamide from the active extracts of Penicillium griseofulvuum mycelium.

The basic structure of echinulin was determined by Quilico and coworkers, who demonstrated by exhaustive degradation studies three isopentenoid units, one in an odd configuration, an indole moiety and an alanine derived DKP.[37] The final structural formula was not obtained until Birch had reported the biological incorporation of labeled isopentene precursors into the compound with no label in the DKP structure.[38] This suggested that the indole ring was tetrasubstituted rather than having substituents at only the 2, 5 and 7 positions. Quilico then reported the c-trp-ala derived structure 15,[39] and Birch substantiated the report by noting the incorporation of tryptophan, labeled at the methylene carbon, into echinulin.[40] The configuration of echinulin was determined as c-L-ala-L-trp derived by ORD comparison with alanyltryptophan anhydrides and synthetic models.[41] An earlier determination of the structure as c-L-ala-D-trp was incomplete.[42] The c-L-L configuration has been substantiated by incorporation studies of radiolabeled c-L-L and c-L-D DKP's in the presence of excess tryptophan which show c-L-ala-L-trp to be a biological precursor of echinulen.[43]

The synthesis of echinulin would involve the avoidance of racemization, with the need for subsequent resolution, strong acids and catalytic hydrogenation. The synthesis of a model which would test the practicality of a synthetic scheme has been reported.[41] Ethyl α-2-indoleisobutyrate was reduced with lithium aluminum hydride, oxidized with acetic anhydride-dimethylsulfoxide mixture, and converted by a Wittig reaction with methylene triphenylphosphine to 3-(2-indolyl-3-methyl)but-1-ene, which by a Mannich reaction with formaldehyde and diethylamine afforded structure 16. Reaction of the Mannich base and N-carbobenzyloxy-L-alanylaminomalonate with sodium hydroxide in refluxing xylene yielded the adduct 17, which was saponified, acidified, decarboxylated, and saponified again to yield the carbobenzyloxy dipeptide. Removal of the protecting group in hydrobromic-acetic acid mixture followed by closure to the DKP in refluxing toluene with azeotropic removal of water yielded two diastereomers which were separated by chromatography over Kieselgel G. The dextrotatory isomer exhibited a negative Cotton effect and an ORD curve almost identical to those of echinulin and c-L-ala-L-trp.

The structure of mycelianamide, a laevatory extract of Penicillium griseofulvum, was determined by degradations to possess a $C_{10}H_{17}$ side chain attached through an ether linkage to a para-substituted phenyl ring.[44] Hydrolysis of the zinc-acetic acid reduction product gave alanine and p-hydroxyphenylpyruvic acid, and a strong absorbtion at 1675 cm^{-1} characteristic of unstrained cyclic amides suggested a DKP derived structure.[45] The alanine moiety has been shown to possess the L configuration[47] and configuration about the double bond is reported as shown in figure 18.[47] The synthesis of DL-deoxymycelianamide has been accomplished by established techniques.[48] DL-Alanylglycine anhydride was converted to the 4'-hydroxybenzylidene-DKP by condensation with p-hydroxybenzaldehyde followed by hydroazenolysis of the N-acetate group. Reaction of geranyl bromide with the potassium salt yielded a compound identical with racemized deoxymycelianamide.

A class of mold metabolites, the 2,5-epidithia-3,6-piperazinediones, has been studied because of the toxicity to animals and possibilities as medicinal agents. Sporidesmins (19), metabolites of the New Zealand fungus Pithomyces chartarum which cause facial eczema in sheep, have been reviewed by Taylor.[49] Gliotoxin (20), from Gliocladium fimbriatum, was the first epidithiapiperazinedione shown to block selectively the process by which viral protein and RNA are synthesized in the infected cell.[50] Chetomin, a metabolite with antibacterial activity from the mycelium of Chetomium cochliodies, has been shown to be an epidithiapiperazinedione derivative although the complete structure is not known. The isolation of gliotoxin and chetomin and partial structures of both are covered by Taylor.[49] Aranotin and its acetyl derivative (LL-s88α) were isolated almost simultaneously by two separate groups from different molds.[51,52]



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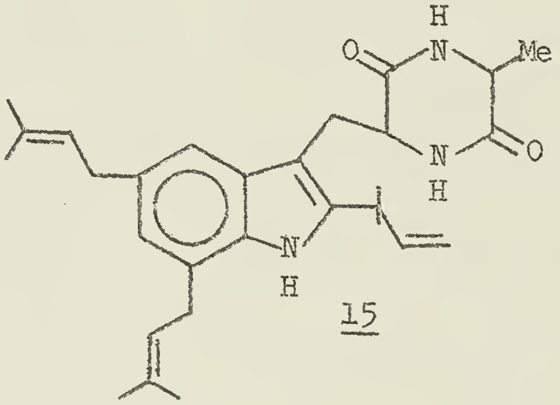

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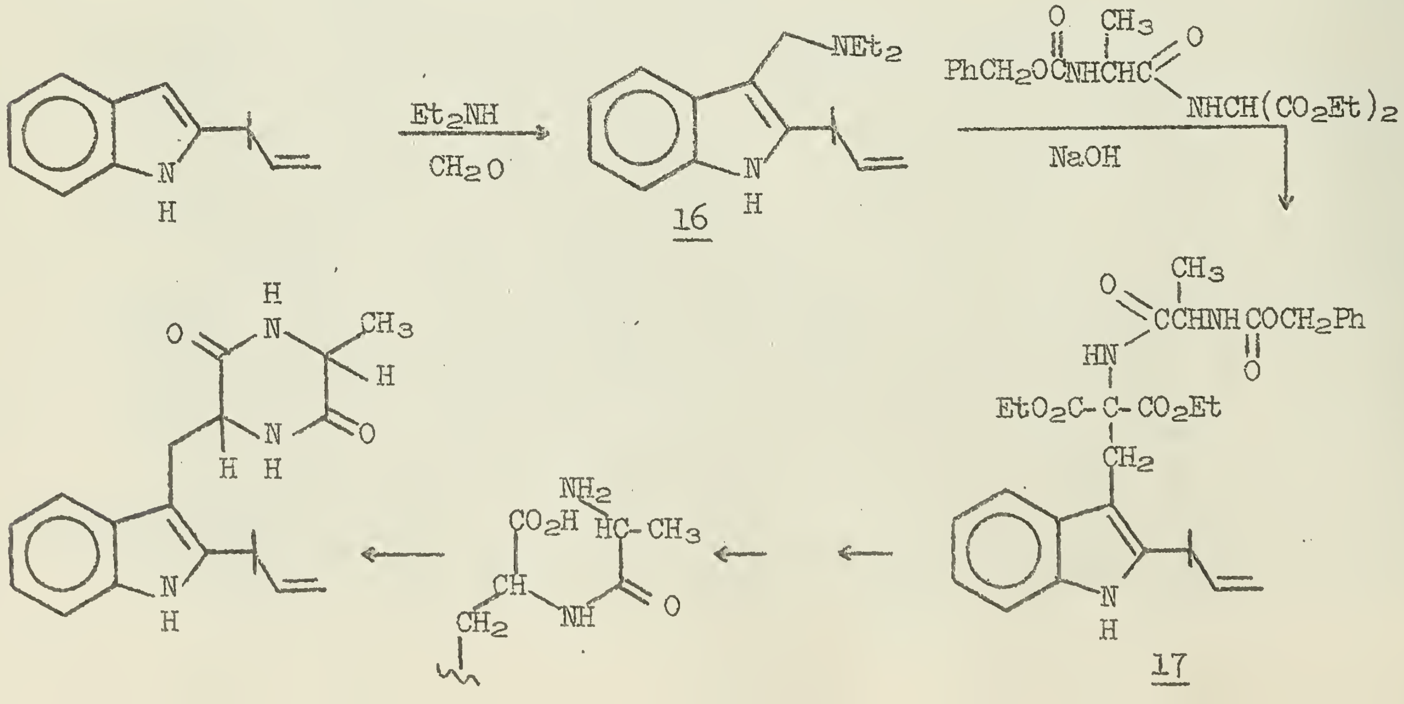

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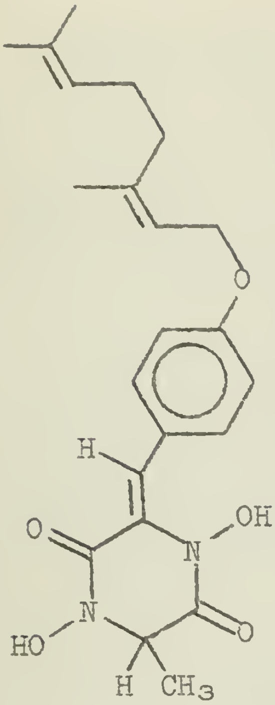

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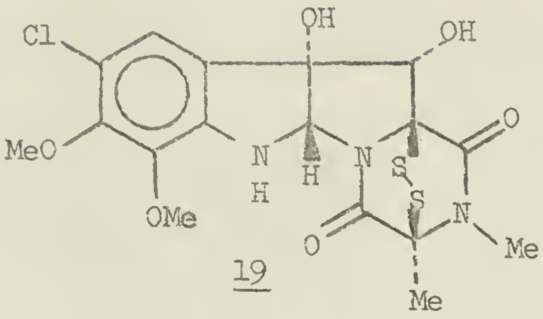

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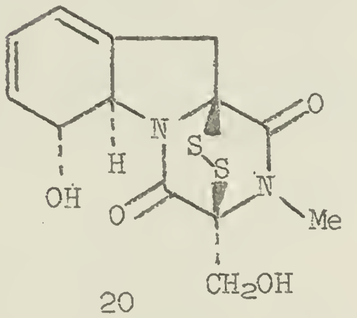

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Gliotoxin is the only epidithia-DKP whose biosynthesis has been studied extensively. Work recorded by Taylor,[49] has suggested that the biosynthesis involves reductive cyclization of a phenylalanylserine derivative. Bose and coworkers have demonstrated the incorporation of phenylalanine to occur by a deaminated pathway and in intact one while glycine may serve as the source of both nitrogen atoms,[53] and that an optically inactive intermediate is involved in the pathway.[54] A recent communication has demonstrated the biological retention of all five aromatic hydrogens from phenylalanine and the lack of incorporation of *o*- or *m*-tyrosine or of 2,3-dopa, thereby eliminating these as possible intermediates.[55] Biosynthesis through a 2,3-epoxide is postulated.

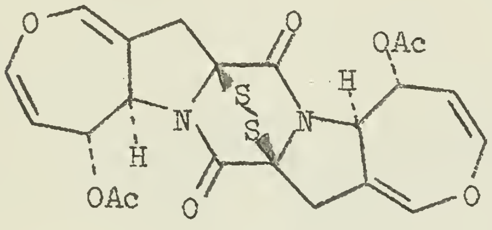
A Lilly group isolated aranotin, acetylaranotin (LL-s88α), and bisdethiodi-(methylthio)-acetylaranotin from *Arachnioetus aureus*, and determined the structure by instrumental methods.[32] Symmetry of the molecule, fortunately distinct chemical shift differences for each of the seven single proton types of the structure, the subsequently separable coupling constant data for each proton; well developed CD data on DKP's and the mass spectral data, which exhibited a facile loss of S_2, suggested the structure 21 (configuration from Ref. 55). Double irradiation studies and chemical methods which did not affect the five core rings strenghtened the postulated structure.

The structure of aranotin was confirmed by X-ray determinations,[55] which allowed a comparison to be made with the X-ray structures of sporidesmin[56] and gliotoxin[57] determined by Fridrichsons and Mathieson. The epidithia-DKP rings are related to c-L-L DKP's, and the C-S-S-C chirality is left-handed for all three compounds. The configuration at the asymmetric bridgehead, the nitrogen bound ring carbon of proline, has the hydrogen away from the disulfide bridge in gliotoxin and aranotin and toward it in sporidesmin. The DKP ring is in the boat form for sporidesmin and gliotoxin, and twisted towards a skewed boat in aranotin because of the strain of the two five-membered rings.

The biological activity of chetomin, sporidesmin and gliotoxin has been shown to be related to the epidithiapiperazinedione structure by lag phase experiments which showed that conditioning to one epidithia-DKP compound provides resistance to another.[58] The epidithia-DKP's have been demonstrated to block selectively and irreversibly the processes by which viral protein and RNA are made within the cell.[48,49,51] Removal of the disulfide bridge destroys the antiviral activity.

The disulfide bridge of epidithia-DKP's can be chemically altered.[59] The bridge of dehydrogliotoxin was converted to a sulfide bridge with triphenylphosphine, and the bridge of sporidesmin was converted to a trisulfide bridge by the action of sulfur and phosphorous pentasulfide in carbon disulfide. The trisulfide bridged compound was reconverted to sporidesmin with triphenylphosphine.

Trown has synthesized the essential core of the epidithiapiperazinediones.[60] Bromination of sarcosine anhydride, substitution of thioacetate and hydrolysis yielded the dithiol 22. Closure to the disulfide bridge with 5,5'-dithiobis-(2-nitrobenzoic acid) yielded the model compound 23, which inhibited the growth of a test virus sixty times the inhibition by gliotoxin or aranotin. The basic anhydrodethio structures for sporidesmin[61] and gliotoxin[62] are available for synthetic attempts directed towards these compounds.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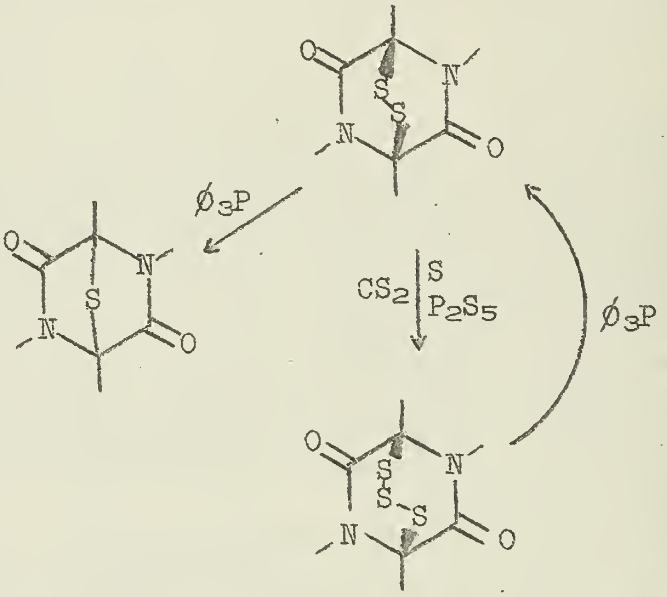

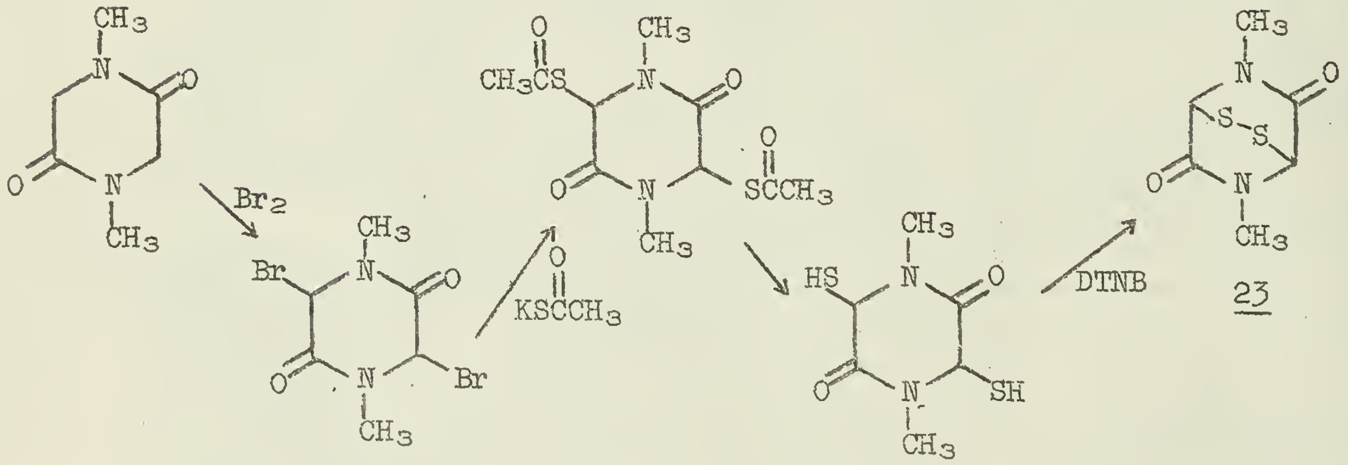

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"CROWN" ETHERS AND RELATED CATION-COMPLEXING MACROCYCLES

Reported by Donald S. Mueller December 10, 1970

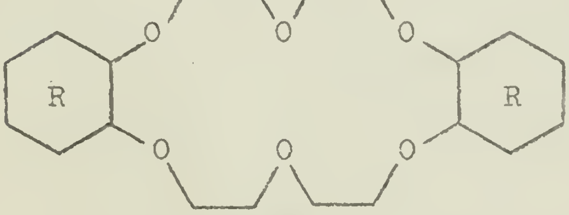
INTRODUCTION

Three years ago DuPont's C. J. Pedersen[1] reported the development of a series of new macrocyclic polyethers with several unique properties and possible applications. Their most outstanding feature is that they form complexes with many different cations and can dissolve inorganic salts in relatively non-polar organic solvents.[2] In addition, selected polyethers show varying degrees of specificity for complexation with the cations studied, most commonly the alkali metals. These salt-polyether complexes are formed by ion-dipole interaction between the cation and the negatively charged oxygen atoms symmetrically arranged in the polyether ring. Stable complexes form when the ionic diameter of the cation and the size of the hole in the polyether ring are complementary so that a "tight-fit" arrangement may be obtained.

The purpose of this seminar will be to describe these polyethers in terms of structure, synthesis, reactivity, and chemical applications. A novel class of similarly structured polythioethers also will be presented, as well as selected macrocyclic antibiotics which appear to function in biological ion transport processes in a molecularly arranged fashion quite similar to Pedersen's polyether-salt complexes.[3,4]

PRODUCT DESCRIPTION AND NOMENCLATURE

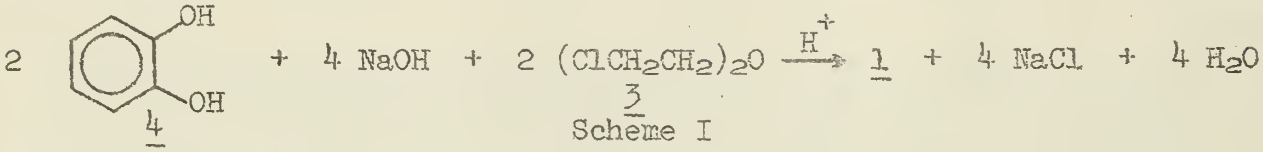
The first "crown" ether to be made was 2,3,11,12-dibenzo-1,4,7,10,13,16-hexaoxacyclooctadeca-2,11-diene (1) which was abbreviated to dibenzo-18-crown-6. The crown designation is given to this series of compounds because of the serrate ring whose conformation brings all the heterocyclic oxygen atoms together into the same plane in a crown-like configuration for chelation of the cation. The abbreviation designates the type and number of hydrocarbon rings, the total number of atoms in the polyether ring, and the number of oxygen atoms in that same ring, respectively. Most reactivity studies undertaken by Pedersen involve 1 or its ring-saturated analog, dicyclohexyl-18-crown-6 (2), the latter existing in both cis and trans isomers. Both 1 and 2 (the mixture) form stable, often crystalline, complexes with all the alkali metal cations to some degree, with some alkaline earth cations, and with a few of the transition metals. However, certain preferences are pronounced, with the monovalent Group I A and B ions being favored generally, and more specifically, potassium. Although numerous other "crown" ethers have been made,[1,5] only 1 and 2 will be discussed because they give the most stable complexes in highest yields.[3]



1, R = aromatic
2, R = alicyclic

SYNTHESIS

Because of the large differences in solubility, crown size, and salts being complexed, no uniform synthetic pathway can be employed in all cases, and five closely related methods have been used to prepare them all. The synthesis of 1 will serve as an example of one common approach (Scheme I). An equimolar amount of bis-(2-chloroethyl)ether (3) is added slowly to a refluxing solution of catechol (4) and NaOH (1:1) in n-BuOH. Acidification causes 1 to precipitate in 45% yield, pure without recrystallization, as determined by mass spectrum, mp, nmr, ir, and elemental analysis.[1]


2
OH
OH
4
+ 4 NaOH + 2 $(ClCH_2CH_2)_2O$ $\xrightarrow{H^+}$ 1 + 4 NaCl + 4 H_2O
3

Scheme I

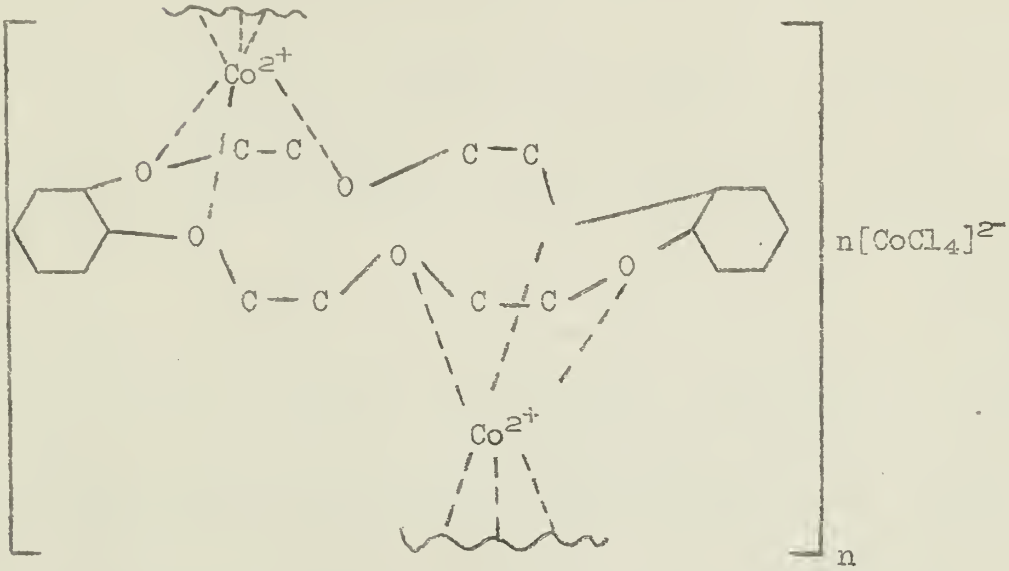
NATURE OF COMPLEXES AND STABILITY FACTORS

Various conditions must be met before stable complexes can be formed. Those important are, (a) the relative sizes of the ion and the hole in the polyether ring, (b) the number of oxygen atoms in the polyether ring, (c) the coplanarity of the oxygen atoms, (d) the symmetrical placement of the oxygen atoms and their basicity, (e) steric hindrance, and (f) the tendency for solvation of the cation, and the charge on that ion.[1] Higher oxygen atom content, with coplanarity and symmetry maintained, and greater basicity contribute to enhanced stability. Strong solvent association prevents complex formation as is evidenced most strikingly by the relative unreactivity of Li^+ when compared with the other alkali metals, the reactivity sequence toward both 1 and 2 being K > Rb > Cs > Na >> Li. Only the most stable complexes form high-melting crystalline solids.

The 1:1 molar ratio supposedly found for all the "crown" ether-Group I cation complexes has recently been shown not to be the only possible combination, as was thought originally.[6] By using an excess of the "crown" ether it was discovered that Rb^+ could also form a 2:1 complex (polyether:salt) with 1 and that Cs^+ formed only a 2:1 or 3:2 complex based on recovery of Cs, on ir, and on preliminary X-ray studies. The 1:1 complex originally proposed for Cs was actually shown to be 2:1 with substantial uncomplexed CsNCS occluded in the crystalline complex. In addition, the originally predicted 4.1 Å hole size of 1 based on van der Waals radii is greatly altered to 2.6-3.2 Å based on a more accurate measurement employing Corey-Pauling-Koltun molecular models. These findings explain why K^+ with a diameter of 2.66 Å will form only a 1:1 complex with 1, while the intermediate diameter of 2.96 Å for Rb^+ can form both 1:1 and 2:1, and the diameter of 3.34 Å for Cs^+ is too large to fit the 1:1 pattern. It is Pedersen's contention that 2:1 ratios indicate "sandwich" complexes, as proposed earlier by Busch[7] and Weiher,[8] and that 3:2 complexes exist in a "club-sandwich" arrangement.

Bright[9] has since suggested that the anions do play an essential role by forming ion pairs with the cation during and after complexation, the relative strength of which is a determining factor in the stability of the complex. This contention may better explain why a few complexes do not dissolve in relatively non-polar solvents. Thermodynamic property studies of these deviate complexes in solution are now underway at DuPont.

Some Group II A and B cations also form complexes, although the multiple ratio complexes predominate over the 1:1. A few transition metals also form polyether-salt complexes as shown most recently by Weiher.[8] He found that Ti^{3+}, V^{3+}, Fe^{3+}, Co^{2+}, and Zn^{2+} all form complexes with 2 which readily dissolve in non-polar solvents. In most of these cases, a color change as well as spectral and solubility changes also denote complexation. It is interesting to note the possible exception of the reaction of $CoCl_2$ with 2. Surprisingly, the composition of the complex formed was independent of the polyether/salt ratio. Also, this complex was insoluble in non-polar solvents while becoming dissociated in polar solvents. Based on magnetic susceptibility data, the value of μ = 5.04 BM indicates an octahedral complex with each molecule of 2 donating only three oxygen atoms to each Co^{2+}. The blue color of the complex and λ_{max} absorptions at 680 and 600 nm also suggest the presence of the $CoCl_4^{2-}$ anion. In accord with these findings, the following polymeric structure (5) was proposed:



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SOLUBILITY EFFECTS

Most solubility studies were conducted in methanol. Aromatic "crown" ethers are only slightly soluble in methanol at room temperature. Therefore, the original discovery of cationic complexation was made when it was noted that the solubility of 1 increased more than forty-fold when an equimolar amount of potassium hydroxide was added to the solution. Since no acidic functionality is present in 1, the result was inexplicable until complexation was recognized. Mass spectral data indicate the presence of dissociated 2-cation and anion. Although all "crown" ethers experience increased solubility after complexation, they are affected to different degrees. For example, Li^+ has the greatest complexing effect on dibenzo-14-crown-4, Na^+ works best for dibenzo-16-crown-5, and K^+ is most effective for 1 and 2. The rationale for this is again primarily dependent upon the polyether hole size relative to cationic diameter.

It was also noted that the electrical conductivity of a salt solution in MeOH decreases when a "crown" ether is added.[1] The conductivity of an 8.8×10^{-3} N methanolic KOH solution decreased from $8.14\ 10^{-4}$ mho/cm to $6.75\ 10^{-4}$ after an equimolar amount of 1 was added. This is probably due to the decreased mobility of the cation after complexation.

The solubilities of the various "crown" ethers and their complexes seem to differ widely, being closely related to the dielectric constant of the solvent. Two criteria can be generalized as guidelines: (a) the solubility tends to be lower the higher the melting point and (b) solubilities of the polyethers are increased in solvents of high dielectric constant and decreased in solvents of low dielectric constant by complex formation. The saturated cyclic polyethers, as a group, are much more soluble in all solvents than the corresponding aromatic compounds. They also have the advantage of being soluble in aprotic solvents, although most are still insoluble in saturated aliphatic hydrocarbons. The only exceptions to aprotic solubility occur when salts of high crystal lattice energy such as K_2CO_3 and KNO_3 are involved. In addition, these salts do not form isolable solid complexes in MeOH.

CHANGES IN UV SPECTRA

All the "crown" ethers containing one or more benzo groups have a characteristic absorption maximum at 275 nm in MeOH, and the shapes of the uv curves are altered in a characteristic manner after complex formation.[10] This method is exemplified by observation of gradual KI addition to 1. Ultraviolet spectra taken at intervals during the constant addition clearly show the development of a second maximum 6 nm to the longer wavelength side of the major one. It is fully formed between ratios of 1.0 and 1.33 moles KI/moles 1. This experiment also showed that even at 2.14 10^{-4} mole/l concentration in MeOH the complex was not significantly dissociated.[1] Na salts added to 1 showed the same new peak appearing but it was less pronounced and not fully formed until a molar ratio of 4:1 was attained. Hence, there appears to be another correlation to complex stability from these observations. The more stable the complex the more pronounced will be its characteristic second uv maximum at lower molar ratios. This has proven true in all cases examined thus far. It should also be noted that with few exceptions no crystalline complex can be isolated from aromatic "crown" ethers when no second maximum is observed in the uv.

The salts employed in these studies covered a broad range of cations and anions. It is noteworthy that although the anions play a decisive role in the solubilization of the "crown" ethers and in the formation of crystalline complexes, they have little effect on uv absorptions at the low concentrations of polyether and large excess of salt most often used as experimental conditions, as long as the salt is completely soluble in MeOH and does not absorb near 275 nm.

Sr^{2+} and Ba^{2+} behave somewhat differently from the Group IA cations with respect to uv absorptions. Their effect is to cause a small hypsochromic shift and decrease the absorbance considerably. They absorb similarly to catechol substrates having electron-withdrawing substituents on the oxygen atoms. It has been postulated that their double charge may be causing this deviation. The only other divalent species tested thus far in this manner is Ca^{2+}, which is too strongly solvated to show any complexation.

Uv data further confirm the superiority of "crown" ethers containing six oxygen atoms separated by ethylene bridges. Coplanarity is best achieved in this case. Smaller macrocycles have a hole size too small for most complexes, while larger rings lose coplanarity and complex the larger cations (Cs^{+}, Ba^{2+}) less effectively than 1 or 2, even though their hole sizes are better suited for these cations.

Polyether 2 does not absorb in the uv above 200 nm and, therefore, cannot be studied similarly to 1. However, its complexing capability relative to 1 may be ascertained by mixing equimolar amounts of 1 and 2 and then checking the uv spectrum for appearance of the characteristic second maximum upon gradual addition of KBr. Under these conditions it is not clearly defined until a ratio of 2.24 polyether/KBr is established, while with 1 alone in solution with KBr the peak appears at a 1.12 molar ratio. This confirms what had been indicated in solubility studies, namely, that "crown" ethers with saturated rings are better complexing agents than their benzo analogs. The reasons for this may be due to the higher basicity of the oxygen atoms or the more easily altered conformation in the alicyclic case.

ISOLATION OF SOLID COMPLEXES

Crystalline etherates were relatively uncommon prior to Pedersen's "crown" complexes. Crystals may be obtained only if the following conditions are met (a) the crystal lattice energy of neither the polyether nor the salt is too high individually, (b) the complexing power of the polyether is very strong, and (c) the solubility of the complex in the mutual solvent is appreciable. Again, different methods were necessary to complex a broad range of "crown" ethers. Because most complexes rapidly dissociate in water only dried solvents were used. Also, heating was avoided when possible, and recrystallizations were generally unsuccessful. This failure appears to be caused by dissociation in the aromatic polyether cases and formation of glassy complexes in the corresponding alicyclic cases. The crystals that have been obtained have sharp melting points when aromatic "crown" ethers are used, but a fairly broad range for the saturated analogs because of the cis-trans isomers. The observed melting points of the complexes are considerably higher than those of the components except for the highly ionic salts.

POLYTHIOETHERS

Since the publication of Pedersen's original work, Busch and Rosen[11-13] have synthesized and complexed several new macrocyclic polythioethers. Much of the work has dealt with low-spin versus high-spin Ni^{2+} complexes. The former are BF_4^- complexes, which are the first reported tetradentate macrocyclic ligands containing only sulfur donor atoms. The latter are Ni^{2+} salts with anions common to those used by Pedersen and will be the only ones considered here.

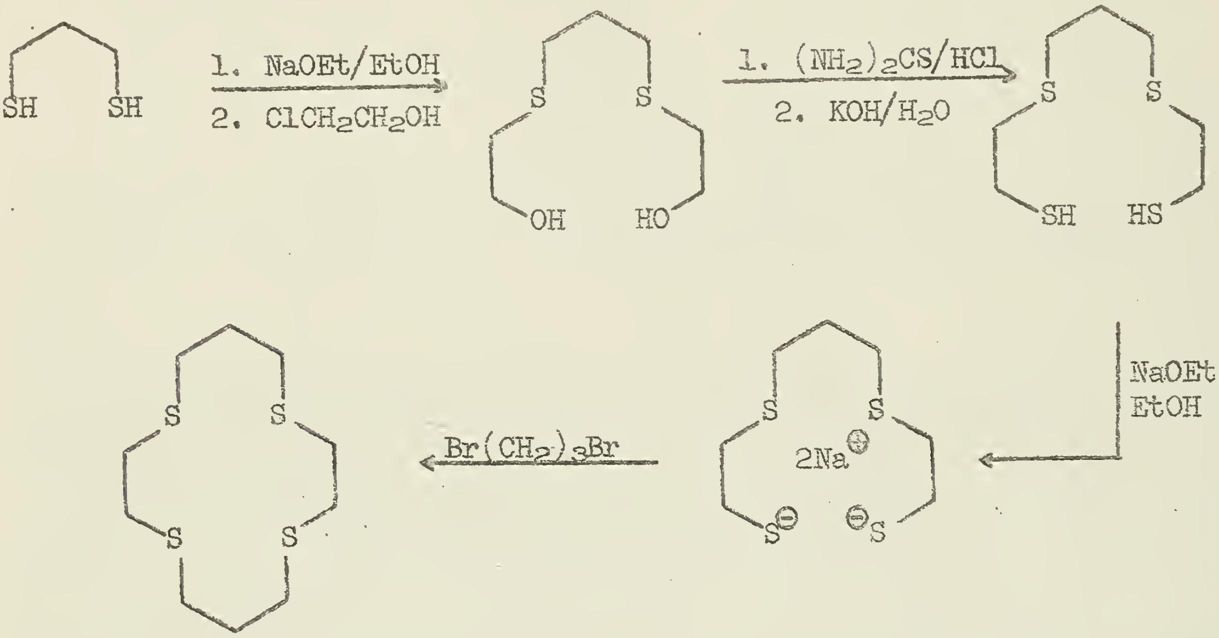
The synthesis of 1,4,8,11-tetrathiacyclotetradecane (6)[11] by the straightforward reactions shown in Scheme II will serve as an exemplary pathway. The structure of the ligands was determined by mass spectrometry which showed them to be monomers, elemental analysis, disappearance of the S-H stretching band in the ir, and by nmr data.

Tetragonal species of the type $Ni(6)X_2$ where X = NCS, Cl, Br, I have been prepared as evidenced by nmr peak shifting to lower field and by the appearance of four discernible bands in the near ir and visible region. The complexes are prepared from the $Ni(6)(BF_4)_2$ complexes by addition of excess salt containing the desired anion. The tetrafluoborate complex was previously prepared from the 1:1:4 addition of 6 to a solution of $Ni(BF_4)_2 \cdot 6\ H_2O$ and Ac_2O in dry nitromethane.[11,13] All the complexes are white, sublimable, paramagentic solids, and all but the iodide are non-electrolytes in nitromethane solution.

It has been shown[12] that tetradentate polythioethers of thirteen or less atoms cannot circumscribe the octahedral Ni^{2+} (μ = 3.0-3.2 BM) and chelate with its sulfur donors in a single plane. Because of this only 3:2 and 2:1 (ligand/Ni^{2+}) complex ratios have been observed for these ring sizes. Compound 6 appears to be a borderline case, with the possibility of a 1:1 complex existing.

Most recently Busch synthesized an octadentate polythioether,[14] 1,4,8,11,15,18,22,25-octathiacyclooctacosane (7) in the same manner that 6 was prepared, but by extracting what was originally thought to be only polymeric residue. Under these conditions the dimer (m/e = 536) is actually favored more than 3 to 1. Complexes of $Ni_2(7)X_4$ where X = BF_4,NCS show a definite 1:2 (ligand/Ni^{2+}) ratio in which four donor atoms are coordinated to each of two Ni^{2+} ions. Complexes showing a new 1:4 ratio have also been prepared with $PdCl_4^{2-}$ and $PtCl_4^{2-}$, the latter of which is so stable that it dissociates only slowly in water. In this case, the ligand appears to act in a bidentate fashion toward each of the four metal ions, resulting in four square-planar metal ions per molecule.

Black and McLean[15] have shown that while polyether 8 forms planar complexes in all cases, the polythioether analog, 9, the first all-sulfur hexadentate ligand, accommodates the six octahedral valence positions of a transition metal ion and forms both Co^{2+} and Ni^{2+} complexes more rapidly because of its higher coordinating ability. It is somewhat surprising to note that a combined thio and oxyether, 10, can form a complex with neither cation.



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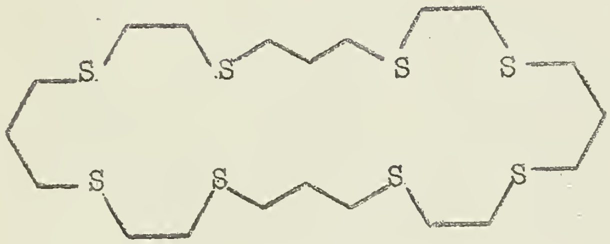
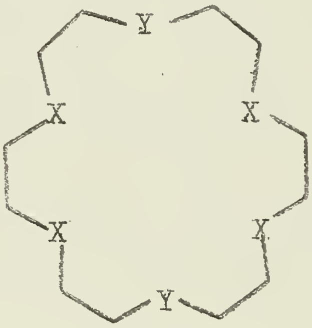
Scheme II



7



8, X = Y = O
9, X = Y = S
10, X = S, Y = O

MACROCYCLIC ANTIOBIOTICS

Several recent papers have presented the concept of macrocyclic antiobiotics acting as ionophores, compounds which induce alkali ion permeability in mitochondrial and other systems by carrying ions across lipid barriers as lipid-soluble complexes.[16,17] Most show a preference for K^+ cations and act as carriers by forming complexes which form and dissociate rapidly, permitting rapid diffusion across membranes as charged or neutral species. More specifically, Shemyakin's work[18,19] deals with conformational changes in the antibiotics to allow for their role as ion carriers. Crystal structure analyses have also been undertaken.[20] In addition, Mueller[21] has dealt directly with Na^+ versus K^+ discrimination in experimental membranes. However, only two articles have appeared pertaining to direct comparisons between "crown" ethers and these antibiotics.[3,22]

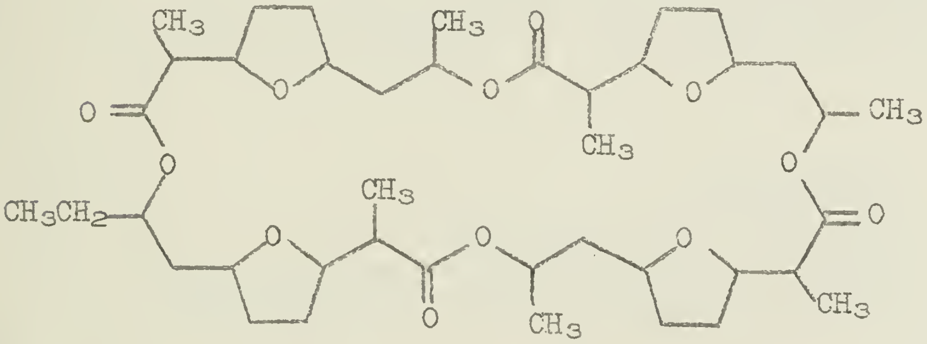
Although the antibiotics valinomycin[16,18] and the enniatins[19,20] have been reviewed in this respect, a comparison of 2 and monactin (11)[22] will serve as our model. Structurally, 11 and 2 appear quite different, but their overall zero net charge, availability of oxygen donor atoms, and large central cavities give the comparison considerable credance.

Eisenman, Ciano, and Szabo[22] developed a series of mathematical equations to express the theoretically expected properties of an ion carrier through lipid membranes. Bilayer membrane potential and resistance as measures of ionic permeabilities were first investigated. In the absence of either 2 or 11 only small potential differences result when KNO_3 is added to one side of a lipid membrane with $10^{-2}M$ KCl or NaCl on both sides. Only a slightly greater transference number for cations than anions was detected. However, when 2 or 11 was then added, considerable cationic permeabilities were noted, although only 11 followed an ideal Nernst slope. Both macrocycles gave the same sequence of permeability: K > Rb > Cs > Na > Li.

Membrane conductance studies based on macrocycle concentration for a given salt concentration indicated that 2 and 11 were related qualitatively but not quantitatively. Here it was found that when 2 was employed the alkali cations affected the conductances in the sequence, Cs > Rb > K > Na > Li, unlike 11 which again gave the theoretically predicted permeability sequence.

Solvent extraction studies were undertaken in CH_2Cl_2 because of its excellent solubilizing power and in n-hexane because of its closer resemblance to the hydrocarbon interior of the lipid bilayer. In both solvents it was shown that association is neglibible between the complexed cation and the anions of the salts in solution. While 11 reproduced its reactivity sequence, 2 gave another new one: K > Rb > Na > Cs > Li.

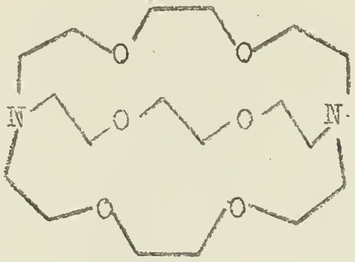
The dissimilar sequence results given for 2, as well as a surprising salt concentration dependence, indicate that 2 is not nearly as suitable an example for a carrier mechanism as is 11, which obeyed the theoretical predictions perfectly. Further investigation to explain the incongruous results shown by 2 are currently underway.



11

RELATED COMPOUNDS AND STUDIES

Dye[23] has studies the solubilization of alkali metals in THF by use of 2 in order to examine new stable solutions of solvated electrons. Smid[24,25] is now involved with the binding of "crown" ethers to ion pairs of carbanion salts to determine contact versus solvent-separated ion pairs. A bicyclic hexadentate polyether, 12, has recently been synthesized and its metal complexes, called cryptates, have been studies in detail.[26-28] Apparently the cryptates function similarly to "crown" ethers by circumscribing the cation in their molecular cavity, but they seem much more stable to water and other unfavorable conditions. Conformational studies are now underway.



12

APPLICATIONS

Several important applications of "crown" ethers have been suggested by Pedersen and may be summarized as follows:[2,29]

(a) the use of certain inorganic reagents in homogeneous organic solvent solutions; e.g. in ester saponifications and $KMnO_4$ oxidations

(b) analysis of organic substrates by dissolving ionic reagents in the organic solvent of the substrate for color reaction or titrations

(c) modifying behavior of materials containing small amounts of undesired cations

(d) separation of different cations

(e) catalysis of solution ionic polymerizations

(f) biochemical studies where the K^+ versus Na^+ rate of permeation through organic membranes is important.

CONCLUSIONS

The relatively new "crown" ethers have already been shown to be a valuable asset to chemists in numerous fields. Their amazing cationic complexing ability merits considerable attention and certainly justifies expanded investigation.

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SYNTHESIS AND REACTIONS OF CERTAIN HIGHLY STRAINED TETRACYCLIC COMPOUNDS

Reported by Kazuyuki Yano December 14, 1970

Part of the study of small ring compounds is concerned with their solvolytic and thermal behavior and their metal-catalyzed isomerizations, which result from the relief of strain energy or geometrical factors. For the published work on bicyclic and tricyclic systems, double bond participation, cyclopropane participation, benzene ring participation, concerted assistance, and relief of strain have been called upon to rationalize the reactivity and the products observed. The relative rates of solvolysis of some model compounds are shown in Chart I. The desire to investigate these effects in a highly defined rigid system led us to synthesize tetracyclo$[3.3.0.0^{4,6}0.^{3,8}]$-oct-2-yl derivatives (1-A, 1-B). Although the parent hydrocarbon was obtained by Freeman and Rao,[1] no derivatives of it were known. Chart II shows a our synthetic scheme. Evidence for the stereochemistry of the epimers (1-A and 1-B) was obtained from their nmr spectra, compared to the bicyclo[2.1.1]hexane system (5-A and 5-B)[2] and the pentacyclo$[4.3.0.0^{2,4}0.^{3,8}0.^{5,7}]$-nonane system (9).[3] Solvolysis of 1-A-OPNB and 1-B-OPNB, and norbornadien-7-yl *p*-nitrobenzoate (3) were carried out in 50% aqueous acetone by titration of the *p*-nitrobenzoic acid produced. The kinetic data are summarized in Table 1. Taking into consideration the ratio of the solvolysis rates of 9-OPNB and 3-OPNB,[3] the ratio of 1-B-OPNB:9-OPNB is 10^{-1}, and 1-B-OPNB is enhanced by 10^{11} compared to 7-norbornyl derivative (2). Wiberg and coworkers[4] attributed the large enhancement of the solvolysis rate of the *endo* isomers (5-B and 6-B) over the respective *exo* isomers (5-A and 6-A) to the geometry of the *endo*, which permits a concerted rearrangement with a disrotatory motion leading directly to relief of strain.[5] The geometry of the *exo* isomers does not allow concerted interaction of the cyclobutyl C-C bond with the developing p-orbital. The difference of the rates of the two *endo* isomers (5-B and 6-B) was explained in terms of the C-C-C bond angle at the reaction site.[4] Since the rate of the *endo* isomer (1-B) is the same order as the *endo* isomer mentioned (5-B) despite the clearly smaller C-C-C bond angle as judged by inspection of models, another factor is required to explain the rate. We suggest that the cyclobutyl ring in 1-B might bend inside more than 5-B, because of the highly strained and rigid system. This bent model easily explains the observed results: the large enhancement of the rate of 1-B over 1-A, the apparent thermal stability of 1-A and 1-B, and no correlation of vibrational frequency with bond angle in cyclobutyl derivatives.[4]

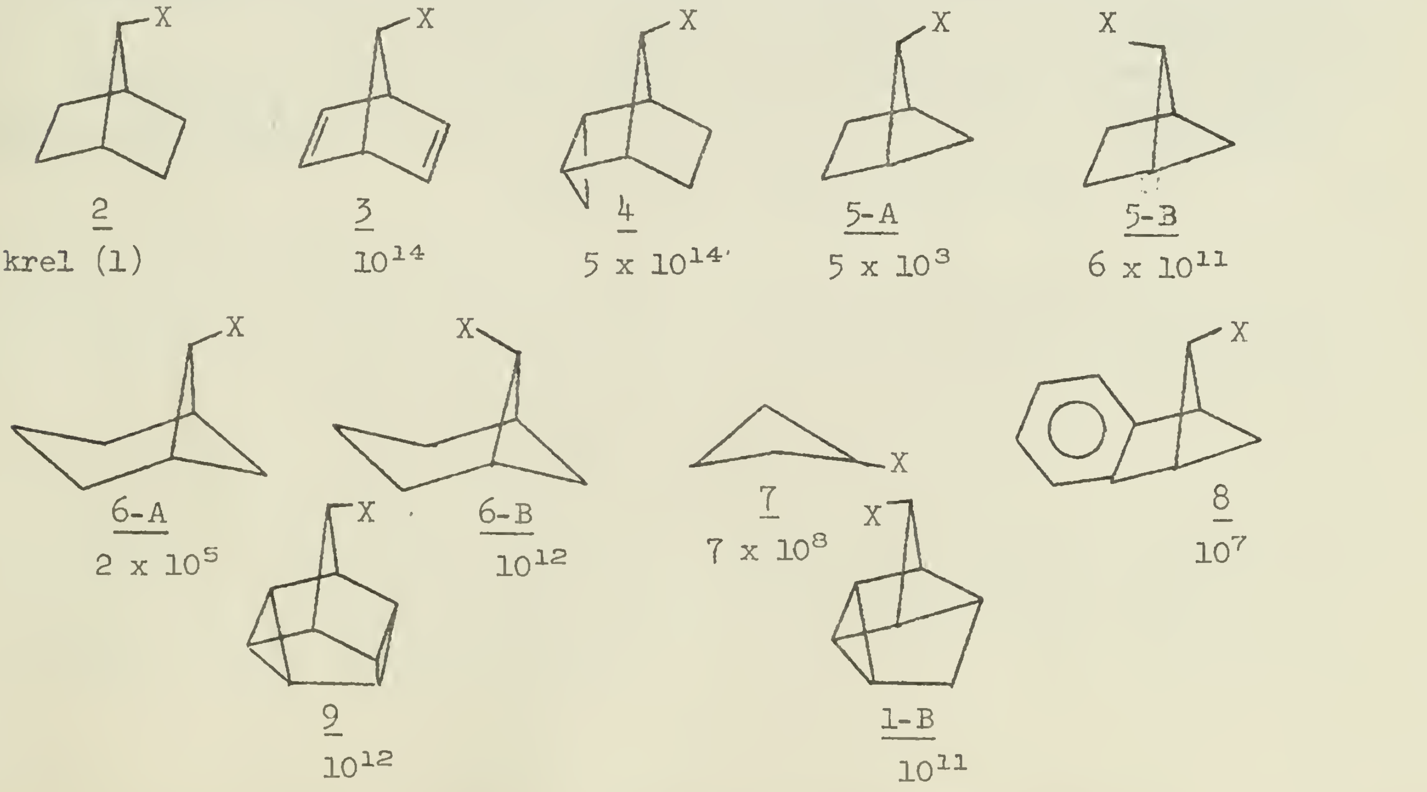

Chart I. Relative Rate of Solvolysis of Some Model Compounds

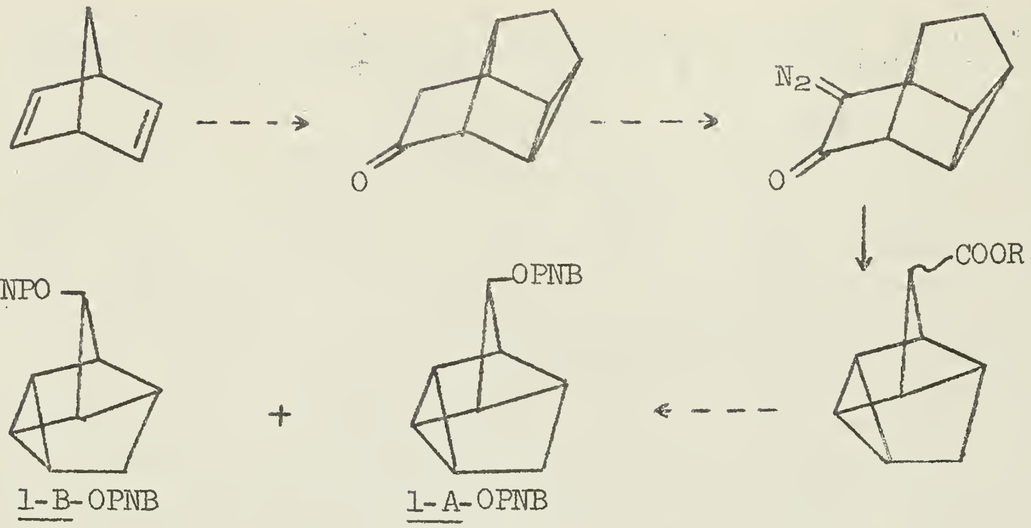

Chart II. Synthesis of 1-A and 1-B

Table 1. Rates of Solvolysis of 1-A, 1-B, and 3 p-nitrobenzoates

Substrate	Solvent	Temp.	k sec^{-1}	$\Delta H^{\ddagger}$ kcal/mol	$\Delta S^{\ddagger}$ eu
endo(1-B)	50% acetone	110°	1.61×10^{-5}	37.2	+14.5
		125°	5.50×10^{-5}		
exo(1-A)		Too slow to be measured			
3-OPNB	50% acetone	110°	7.30×10^{-4}		
		125°	3.04×10^{-3}		

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POLYLITHIATED ACETYLENES AND NITRILES

Reported by Martin E. Newcomb December 17, 1970

Within the last few years, various compounds containing carbon-carbon or carbon-nitrogen triple bonds have been polylithiated. The area is of current research interest, and some potentially useful synthetic applications have been demonstrated or may be envisioned. This seminar covers the formation of polylithio compounds, products formed by their derivatization, and preliminary results on their structures.

GENERAL

Polylithio compounds are formed by metal-hydrogen exchange with alkyllithiums. Recognition of the catalytic properties of alkoxides[1] and chelating diamines[2] for these reactions has proven useful. Lithioacetylenes or -nitriles generally lead to good yields of products formed by protonation, coupling, addition to carbonyls, and carbonation, the acetylenes forming acetylenes or allenes and the nitriles forming nitriles, ketenimines or ynamines. Evidence of polylithiation is found directly from nmr or ir studies, from the stoichiometry of the gas evolved from the protonated base, or may be inferred from products formed by the polylithio compound. The latter method is frequently unsound since the coupling reaction with chlorotrimethylsilane, which is frequently used, is not faster than metalation[3,4], and it is possible that lithio species could couple and then metalate to form polysubstituted products in a stepwise manner. The observation that silicon increase acidity of α-hydrogens[3,4,5] shows that inferred polylithiation by the use of polysilylated products is precarious.

POLYLITHIOACETYLENES

The simplest polylithioacetylene, dilithium acetylide (C_2Li_2), is formed by heating lithium and graphite above 850°.[6] C_2Li_2 has found limited synthetic use in the production of ethynols.[6]

The parent alkyne of the series is propyne (1). West, Carney, and Mineo[7] initiated current interest in this species with the report of formation of the tetralithio compound (C_3Li_4). Further reaction with chlorotrimethylsilane (Me_3SiCl) led to acetylene 2 and allene 3. It was assumed that steric bulk

$$\underset{\underline{1}}{HC{\equiv}C\text{-}CH_3} \xrightarrow[\text{2) } Me_3SiCl]{\text{1) } \underline{n}\text{-}BuLi} \underset{\underline{2}}{(Me_3Si)_2CH\text{-}C{\equiv}CSiMe_3}(50\%) + \underset{\underline{3}}{(Me_3Si)_2C{=}C{=}C(SiMe_3)_2}(25\%)$$

of the Me_3Si- groups favored the formation of the allene. In a later study,[8] West and Jones showed that the yield of 3 varied with change in the solvent added during the derivatization. Thus, adding tetrahydrofuran (THF) increased the yield of 3 to 70-75%. This effect was explained by an increased rate in the coupling of intermediate 4 with Me_3SiCl and thus a diminished reaction of

$$\underset{\underline{4}}{(Me_3Si)_3C_3Li}$$

4 with ethereal solvent to produce 2. To determine the cause of the formation of allenic 3, intermediate 4 was generated from 2 or 5 and then treated with water, methyl iodide, or Me_3SiCl to give various acetylenic and allenic products. It was concluded that 4 behaved as an ambident anion, and product distribution reflected steric control.

$$\underline{2} \xrightarrow{110^{\circ}} \underline{2}\ (40\%) + \underset{\underline{5}}{(Me_3Si)_2C{=}C{=}CH(SiMe_3)}\ (60\%)$$

$$\begin{tikzcd}
\underline{2}\ (\text{or } \underline{5}) \arrow[r, "n\text{-}BuLi"] & \underline{4} \arrow[r, "Me_3SiCl"] \arrow[dl, "H_2O"'] \arrow[d, "MeI"] & \underline{3}\ (100\%) \\
\underline{2}\ (41\%) + \underline{5}\ (57\%) & \underset{\underline{6}}{(Me_3Si)_2(Me)C\text{-}C{\equiv}C(SiMe_3)}\ (30\%) + \underset{\underline{7}}{(Me_3Si)_2C{=}C{=}C(Me)(SiMe_3)}\ (45\%) &
\end{tikzcd}$$

Tetrasilylated allenes have been produced via other lithiation reactions. Jaffe[4] prepared 3 and other products in the reaction of allene with n-BuLi followed by derivatization with Me_3SiCl. Due to short reaction time, low temperature, and high yield of 1,3-bis(trimethylsilyl)propyne, a dilithium species was proposed. Surprisingly, in a competitive reaction, 3 was formed when n-BuLi was added to allene in the presence of Me_3SiCl. Gilman and his co-workers[9] identified 3 in their lithiations of some perhalobenzenes and mono- or bis(trimethylsilyl)perhalobenzenes.

Studies on butynes have been reported by two groups. Eberly and Adams[10] found that 1-butyne (8) reacted with n-BuLi to produce a dilithium species which, upon carbonation and reduction, yielded 2-methylglutaric acid (9).

$$\underset{\underline{8}}{HC{\equiv}C\text{-}CH_2CH_3} \xrightarrow[210\ hr.]{2\ n\text{-}BuLi} \xrightarrow[2.\ H_2]{1.\ CO_2} \underset{\underline{9}}{HO_2C\text{-}CH_2\text{-}CH_2\text{-}CH(Me)\text{-}CO_2H}\ (39\%)$$

Similarly, 1,2-butadiene produced 9. West and Jones[8] showed that t-BuLi was a sufficiently strong base to abstract three protons from 1-butyne, as indicated by the evolution of three equivalents of isobutane, whereas the identical reaction with n-BuLi produced only two equivalents of butane. Derivatization of trilithiobutyne with Me_3SiCl gave tris(trimethylsilyl) products 6 and 7.

$$\underline{8} \xrightarrow{3\ t\text{-}BuLi} C_4H_3Li_3 \xrightarrow[THF]{Me_3SiCl} \underline{6}\ (35\%) + \underline{7}\ (65\%)$$

In both studies, 2-butyne was found to be unreactive to the conditions employed for the reaction of 1-butyne.

Klein and Gurfinkel[11] reported lithiations of octadecynyl alcohols (10a) and methyl ethers (10b). Both mono- and dilithiation of a propargyl group occurred.

$$CH_3(CH_2)_{15-x}C{\equiv}C(CH_2)_xOR$$

$$\underline{10};\ x = 4\text{-}10;\ \underline{a},\ R = H;\ \underline{b},\ R = Me$$

Products were recovered after carbonation, the monoacids being allenic and the diacids acetylenic with both carbonyls on the same carbon. In general, proton abstraction was random from C_x or C_{x+3}, but the second proton abstraction was always from the same carbon as the first.

In a logical expansion of their studies, Chwang and West[12] have formed the tetralithio derivative (11) of 1,3-pentadiyne (12) using tetramethylethylenediamine (TMEDA) as a catalyst. Protonation of 11 produced C_5H_4 isomers 12-14. Derivatization of 11 with Me_3SiCl[13] led to the unusual tetrasilylated derivative of 14, (15), and lower silylated products.

$$\underset{\underline{12}}{HC{\equiv}C\text{-}C{\equiv}C\text{-}CH_3} \xrightarrow[TMEDA]{n\text{-}BuLi} \underset{\underline{11}}{C_5Li_4} \xrightarrow{H_2O} \underline{12}\ (5\%) + \underset{\underline{13}}{HC{\equiv}C\text{-}CH_2\text{-}C{\equiv}CH}\ (20\%)$$

$$+ \underset{\underline{14}}{HC{\equiv}C\text{-}CH{=}C{=}CH_2}\ (15\%)$$

$$\underline{11} \xrightarrow[\text{THF}]{Me_3SiCl} \underset{\underline{15}}{(Me_3Si)C{\equiv}C\text{-}C(SiMe_3){=}C{=}C(SiMe_3)_2} \quad + \quad \text{other products}$$

Phenylpropynes have been studied by three groups. Mulvaney, Folk and Newton[14] first reported that 1-phenylpropyne (16) isomerized to 3-phenylpropyne (17) when treated with n- or t-BuLi followed by protonation. They also reported that addition of D_2O

$$\underset{\underline{16}}{PhC{\equiv}C\text{-}CH_3} \xrightarrow{BuLi} \xrightarrow{H_2O} \underset{\underline{17}}{PhCH_2\text{-}C{\equiv}CH}$$

to the polylithio species produced mainly 17-d_3. Since D_2O was added to the lithiated species, the inference of trilithiation may be in doubt; however, West and Gornowicz[15] have shown that severe metalating conditions lead to abstraction of up to seven protons from 16. By varying conditions,

$$\underline{16} \xrightarrow[\text{neat}]{50\ n\text{-BuLi}} \xrightarrow{D_2O} \begin{matrix}\underline{16}\\ +\\ \underline{17}\end{matrix} \quad (\underline{d}_3, 5\%; \underline{d}_4, 12\%; \underline{d}_5, 36\%; \underline{d}_6, 37\%; \underline{d}_7, 8\%)$$

West and Gornowicz were able to produce nine silylated propynes and allenes from 16, containing from one to five trimethylsilyl groups, in which ring silylation was analogous to that in toluene[16]. Klein and Brenner[17] produced mono-, di- and trilithio compounds from 16, 17 and phenylallene (18). They found that monolithiation of 16 produced 19 which further reacted to give 16 and 20. Dimetalation of 17 or 18 led to dilithio product 21, possessing a pmr spectrum different from 20. Trimetalation of 16 or 17 produced the trilithio product 22. It was noted that

$$\underline{16} \xrightarrow[\text{ether}]{1\ n\text{-BuLi}} \underset{\underline{19}}{PhC{\equiv}C\text{-}CH_2Li} \longrightarrow \underline{16} + \underset{\underline{20}}{PhC{\equiv}C\text{-}CHLi_2}$$

$$\underline{17} \text{ or } \underset{\underline{18}}{PhCH{=}C{=}CH_2} \xrightarrow[\text{ether}]{2\ n\text{-BuLi}} \underset{\underline{21}}{PhCH(Li)\text{-}C{\equiv}CLi}$$

$$\underline{16} \text{ or } \underline{17} \xrightarrow[\text{ether}]{3\ n\text{-BuLi}} \underset{\underline{22}}{PhC_3Li_3}$$

deuteration of 20 and 21 led to the same product, 23. Since 20 is stable in solution, a hydrogen transfer from C_3 to C_1 must be accounted for during the

$$\underline{20} \xrightarrow{D_2O} \underset{\underline{23}}{PhCHD\text{-}C{\equiv}CD} \xleftarrow{D_2O} \underline{21}$$

deuteration. The authors postulate a [1,3] sigmatropic shift involving six electrons; however, since they deuterated by adding D_2O to the basic solution, their results are in question, as reaction between monodeuterated species is possible. Also, West and Gornowicz[15] claim on the basis of ir that the dilithio species has an allenic structure (see Table 2 below). This discrepancy may be due to a difference in solvents. It is of interest to compare the silylated products of Klein and Brenner[17] with some of those of West and Gornowicz[15]. The results in Table 1 illustrate the effect of changing solvent.

Table 1. Products from lithiation and derivatization of phenylpropynes[15,17]

<table>
<tr><th rowspan="2">starting material</th><th rowspan="2">equiv. n-BuLi</th><th colspan="6">% products[a]</th></tr>
<tr><th>16</th><th>24</th><th>25</th><th>26</th><th>27</th><th>28</th></tr>
<tr><td>16[b]</td><td>1</td><td>43</td><td colspan="2">16</td><td></td><td>40</td><td></td></tr>
<tr><td>16[c]</td><td>1</td><td></td><td></td><td></td><td>50</td><td>some</td><td></td></tr>
<tr><td>16 or 17[b]</td><td>2</td><td>10</td><td></td><td></td><td></td><td>90</td><td></td></tr>
<tr><td>16[c]</td><td>2</td><td></td><td></td><td></td><td>15</td><td>70</td><td>15</td></tr>
<tr><td>16 or 17[b]</td><td>3</td><td></td><td></td><td></td><td></td><td></td><td>100</td></tr>
<tr><td>16[c]</td><td>3</td><td></td><td></td><td></td><td></td><td>20</td><td>60</td></tr>
<tr><td>26[d]</td><td>2</td><td></td><td></td><td>33</td><td>67</td><td></td><td></td></tr>
</table>

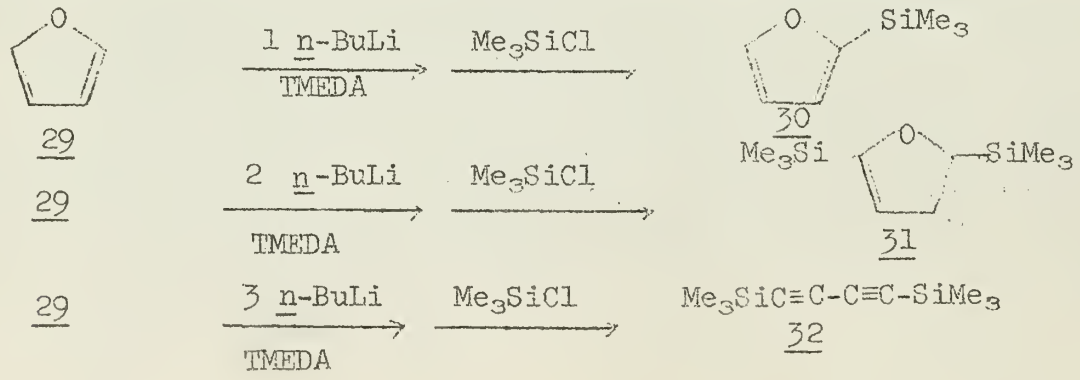
[a] Estimated by glpc. [b] Ref. 17, ether solvent, derivatized with Me_3SiCl. [c] Ref. 15, hexane solvent with ca. 4:1 n-BuLi/TMEDA, derivatized with Me_3SiCl. [d] Ref. 15, hexane solvent, derivatized with H_2O.

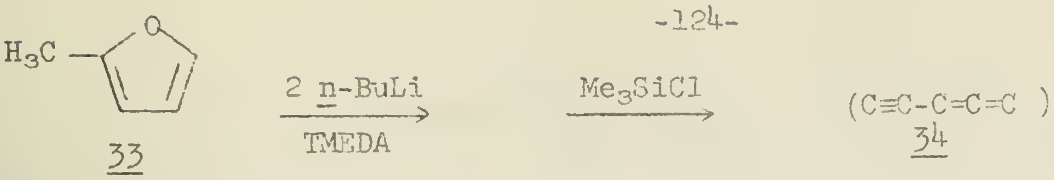
$PhC{\equiv}C{-}CH_2(SiMe_3)$ 24 $PhCH{=}C{=}CH(SiMe_3)$ 25 $PhCH_2{-}C{\equiv}CSiMe_3$ 26

$PhCH(SiMe_3){-}C{\equiv}CSiMe_3$ 27 $PhC(SiMe_3){=}C{=}C(SiMe_3)_2$ 28

Recently Köbrich and Merkel[18] have produced the dilithio derivative of dicycloproplyacetylene. Product studies after carbonation or coupling indicate that metalation occurred at both of the carbons adjacent to the triple bond.

An alternate route to polylithioacetylenes employs vinyl ethers. Erikson[19] found that furan (29) forms the expected products (30,31) when treated with one or two equivalents of base and derivatized with Me_3SiCl. Treatment of 29 with a greater amount of base yielded the biacetylene 32 and no 2,3,5-tris(trimethylsilyl)furan. Similarly, 2-methylfuran (33) loses the oxygen atom when treated with two equivalents of base to give, after derivatization, a product (34) which contains allenic and acetylenic groups by ir but has not been identified as yet. Erikson



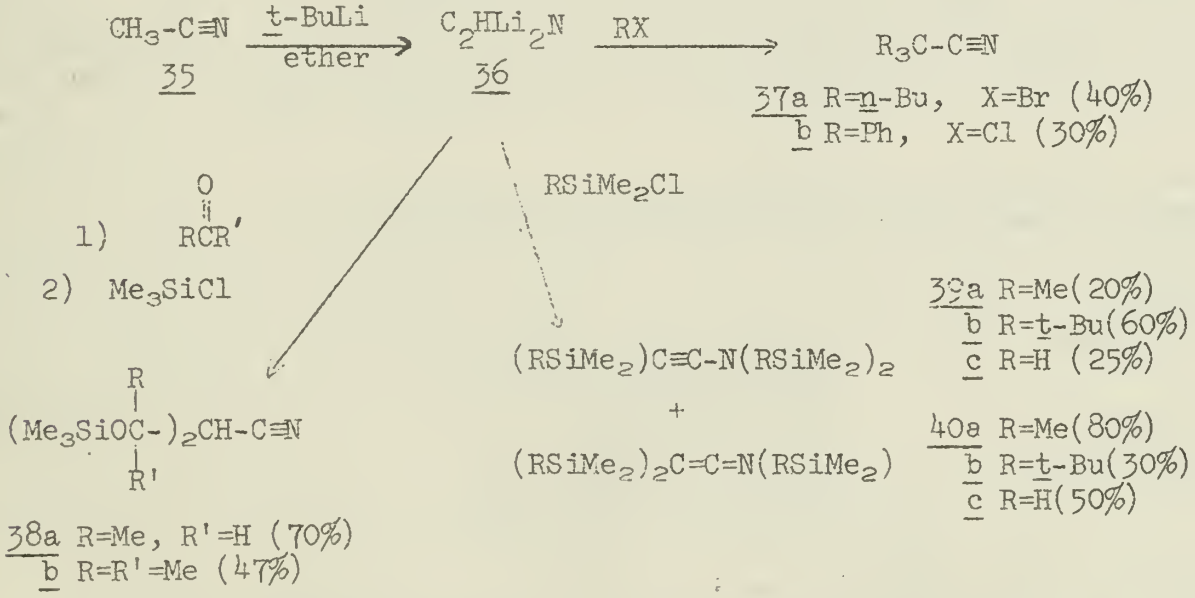


postulated that vinyl ethers eliminate the oxygen following β-hydrogen abstraction, and that furans act as divinyl ethers. In support of this, 2,3-dihydropyran opens to form a product containing a triple bond and a hydroxyl group when treated with two equivalents of base. It is interesting to note that West's product 15 may be similar to Erikson's 34.

POLYLITHIONITRILES

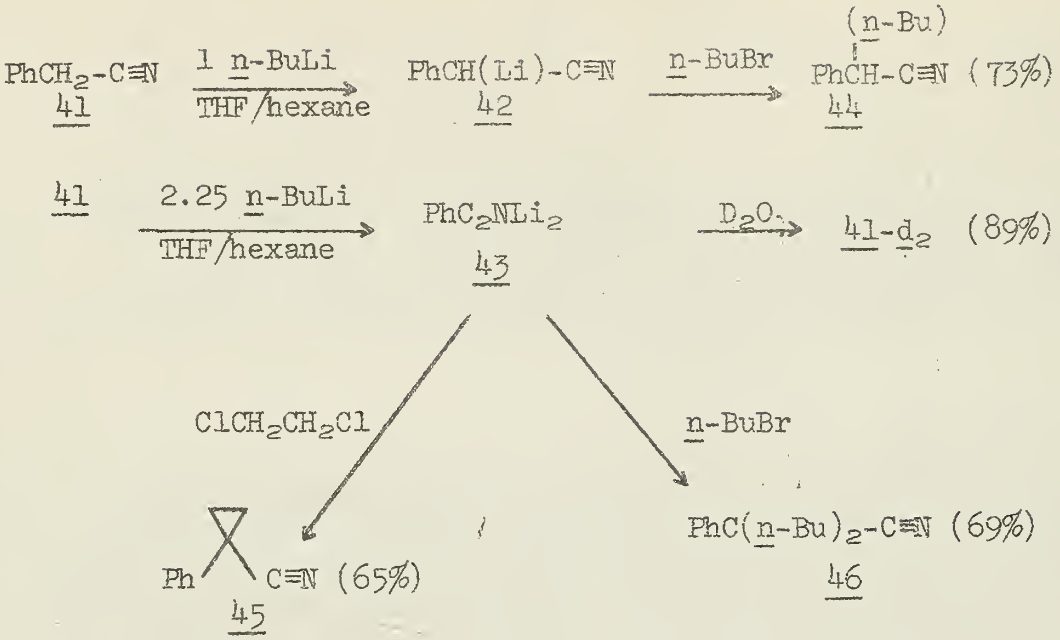
Polylithiation of nitriles and the products from these polylithio compounds reflect the chemistry of analogous acetylenes. The nitrile group, however, is more labile to addition of the alkyllithium. Alkynes mentioned above were metalated by alkylithiums; however, Mulvaney *et al.*[20] have shown that diphenylacetylene, which does not contain relatively acidic protons, added alkyllithiums across the triple bond. Alkylacetonitriles similarly give high yields of addition products with *n*-alkyllithiums.[21]

Acetonitrile (35) has been studied extensively by Gornowicz and West.[22] Their work has shown that previous studies[23] were in error in assigning trimetalated acetonitrile as an intermediate when trisubstituted products were obtained after coupling. Two protons may be abstracted from 35 to form the dilithio species 36. This dilithio compound could be used to form various products. The ynamines (39) were thermally unstable and rearranged quantitatively to ketenimines (40) on heating.



Although Gornowicz and West[22] could not obtain good yields of metalated propionitrile, trimethylsilylacetonitrile was dilithiated and bis(trimethylsilyl)acetonitrile was monolithiated, reflecting the increased acidity caused by the silyl group.

Kaiser and Hauser[24] have produced the mono- and dilithio derivatives (42,43) of phenylacetonitrile (41). These compounds may be of synthetic utility, as shown by the formation of 44, 45, and 46.

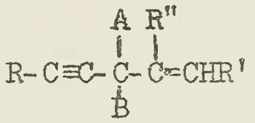


STRUCTURE OF POLYLITHIO SPECIES

Information about the structural characteristics of polylithio acetylenes and nitriles has been gathered by two methods. West's group[8,15,22] has studied ir solution or suspension spectra in the region 2300-1600 cm^{-1}. while Klein and Brenner[25] have studied pmr spectra in perdeuteroether.

A compilation of ir data is presented in Table 2. Structural assignments of lithiated species are those given by West *et al*. In general, lithiation lowers the frequency of the absorbance. The data suggest that no polylithio species maintained a triple bond in its skeleton, and it may be concluded that more favorable bonding is achieved by allenic species when more than one lithium atom is on the propargyl group.

Klein and Brenner[25] have obtained similar conclusions from their pmr work. In metalating the series of 1,4-enynes 47



$$R-C\equiv C-\overset{A}{\underset{B}{C}}-\overset{R''}{C}=CHR'$$

47 A=B=H
48 A=Li, B=H
49 A=B=Li

a R=Ph, R'=Me, R"=H
b R=Ph, R'=H, R"=Me
c R=R'=Ph, R"=H
d R=Ph, R'=R"=H
e R=*t*-Bu, R'=H, R"=Me
f R=*n*-hex, R'=H, R"=Me

they observed that the monolithio species 48 behaved as delocalized anions, as evidenced by the upfield shift of the vinylic protons corresponding to shifts seen in other anions (*i.e.* pentadienyllithium[26]). The shifts, however, were smaller, and it was inferred that delocalization was less. Abstraction of the second propargylic proton to produce 49 led to a downfield shift of the vinylic protons. Since the protons of R remained unchanged from 47 to 49, it was concluded that 49 contained greater charge localization in the propargylic group than 48. Klein and Brenner explained this by the formation of two three-center-four-electron bonds on the propargyl carbons, coining the term "sesquiacetylene" for this system and "sesquiazacetylene" for the analogous nitrile case. This argument presupposes that the dilithio species is dianionic which remains to be proven; however, Gornowicz and West[22] do not

Table 2[a]. Ir absorbances in the region 2300-1600 cm^{-1}.[8,15,22]

			ν, cm^{-1}		
Skeleton	Li_0	Li_1	Li_2	Li_3	Li_4
$C\equiv C-C$	2130	2050 ↘			
$C=C=C$	1970	1890[b]	1870	1770	1675
$C-C\equiv CSiMe_3$	2190 [↘]	[↘]			
$C=C=CSiMe_3$				1770	
$Me_3SiC-C\equiv SiMe_3$	2190 →				
$Me_3SiC=C=CSiMe_3$		1870	1790		
$(Me_3Si)_2C-C\equiv CSiMe_3$	2185 →				
$(Me_3Si)_2C=C=CSiMe_3$	1900	1850			
$PhC\equiv C-C$	2256, 2221[c] →				
$PhC-C\equiv C$	2130[c]	2050 →			
$PhC=C=C$	1925[d]		1900	1780	
$PhC-C\equiv CSiMe_3$	2180 →				
$PhC=C=CSiMe_3$	1925	1870	1790		
$Ph(SiMe_3)C-C\equiv CSiMe_3$	2160	2000 ⇅			
$Ph(SiMe_3)C=C=CSiMe_3$	1900	1850			
$C-C\equiv N$	2230, 2260[e]	2130 ⇅			
isomer of CH_3CN?		2040 →			
$C=C=N$			1820		
$MeC-C\equiv N$	2220[f]	[↘]			
$MeC=C=N$			1880		
$Me_2C-C\equiv N$	2220[g]	2000			
$PhC-C\equiv N$	2250[h]	[↘]			
$PhC=C=N$			1900		
$Me_3SiC-C\equiv N$	2230	[↘]			
$Me_3SiC=C=N$			1900		
$(Me_3Si)_2C-C\equiv N$	2180	2000			

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[a] Arrows represent skeletal rearrangement as lithiation increases, brackets represent predicted behavior. [b] Ref. 4. [c] I. Iwai, H. Shindo, Y. Okajima, T. Konotsune and K. Tomita, Yakugaku Zasshi, 80, 1588 (1960). [d] L. Piaux and M. Gaudemar, Bull Soc. Chim. Fr., 1956, 794. [e-h] Sadtler Standard Spectra 269, 190, 10652, 2231 respectively.

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exclude the possibility of sesquiazacetylene structure for their dilithionitriles. It would be interesting to know the ir spectrum of Chwang and West's C_5Li_4,[12] which would probably be of structure 50 or 51.

$Li_2C=C=C=C=CLi_2$ — 50

$LiC\equiv C-C(Li)=C=CLi_2$ — 51

In conclusion, the polylithio acetylenes and nitriles which have been produced recently may be of synthetic utility. Clarification of the structural properties of these polylithium compounds will require further study.

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REACTIONS OF ORGANOTIN HYDRIDES WITH UNSATURATED SYSTEMS

Reported by Robert J. Hauri January 4, 1971

INTRODUCTION

The first uncatalyzed addition of organotin hydrides, R_3SnH, to olefins was reported by Van der Kerk and co-workers in 1956.[1,2] The synthetic aspects of hydrostannation reactions were discussed comprehensively in 1964[3,4] and briefly in later reviews on tin hydride chemistry.[5,6] Recently, a book on organotin chemistry was published covering the literature through 1968.[7] It is the purpose of this seminar to discuss the mechanism of the hydrostannation reaction with respect to olefins, dienes, and α, β-unsaturated systems.

ADDITION TO OLEFINS

Organotin hydrides having the formula R_3SnH where R = alkyl (or aryl) will add to terminal and internal olefins, forming trialkylstannyl derivatives of the olefin. The reactions may proceed either by a free radical route[3,4,8] or by an ionic pathway.[9] There is considerable evidence to indicate that certain alkynes having strong electron withdrawing substituents react exclusively by an ionic mechanism,[10-13] but these will not be discussed in this seminar.

Van der Kerk and co-workers[1] reported the uncatalyzed addition of both triphenyltin hydride, Ph_3SnH, and tributyltin hydride, Bu_3SnH, to compounds having structure 1 and obtained only the β-stannyl adducts, 2, in high yield. With the exception of crotononitrile, R' = Me, all substrates studied were terminal olefins. The reactions, run in the absence of solvent and catalyst, gave yields generally in excess of 75%. Del Franco et al.[14] were able to add Ph_3SnH to the 1-carbon of various long chain terminal olefins only if the reactions were catalyzed by either azobisisobutyronitrile, AIBN, or uv irradiation. By using excess olefin and heating at 25-50° for 18 hr, under irradiation, the yield of alkyltriphenyltin product was quantitative.[14] The use of either AIBN or uv irradiation generally has been found to significantly increase yields in hydrostannation reactions involving terminal olefins.

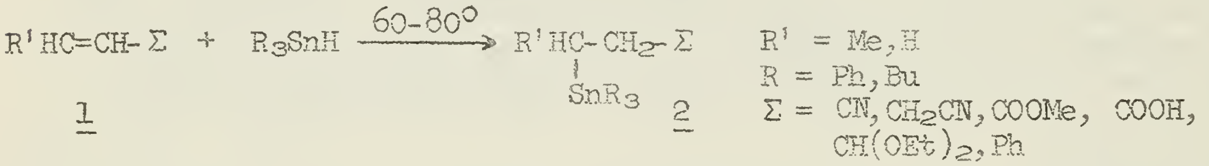
A catalytic route to hydrostannation of olefins was employed by Neumann to add Bu_3SnH to 1-octene, 4-vinylcyclohexene, and α-methylstyrene.[15] Small amounts of $(\text{iso-}C_4H_9)_2AlH$ or $(C_8H_{17})_3Al$ were used to catalyze addition of the stannyl group to the terminal position of the olefin. Without catalysts, these addition reactions for the most part did not go.

In early studies, internal olefins were found to add organotin hydrides slowly or not at all. Neumann[16] attempted to add Et_3SnH to cyclohexene using AIBN as a catalyst but failed to isolate any 1:1 adduct. Clark and Kwon[17] reported that Me_2SnH_2 would not add to 2-butene under uv irradiation. Other studies by Del Franco and co-workers[14] revealed similar findings. Both cyclopentene and cyclohexene would not react with Ph_3SnH under irradiation, the only product observable being hexaphenylditin formed by coupling of two Ph_3Sn radicals.

Kuivila[18] found that it was possible to add organotin hydrides to internal olefins, including cyclohexene which had previously been unreactive,[16] by irradiation at 10-15°. It was theorized that in the earlier work the N=N bond of AIBN competed more effectively for organotin hydride than did the olefin. Kuivila also showed that the 1:1 adducts formed were consistent with radical attack at the carbon atom which would result in the more stable intermediate radical.

The additions of tin hydrides to olefins not containing strong polarizing groups is accepted to be a free radical process in view of the evidence accumulated. The reactions are accelerated by either uv irradiation or radical initiators and are retarded or stopped entirely by radical scavengers such as galvinoxyl. Also, dependence on solvent polarity is not pronounced, offering further evidence that a radical pathway is operative.

A free radical mechanism has been postulated for the catalytic addition of organotin hydrides to terminal olefins.[3] The reversibility of step (4) has been proven[19] by an isomerization experiment involving deuterated hexenes. Other workers[20] have since shown that the attack of stannyl radicals to unsubstituted α-olefins is indeed a reversible process.



$$\underset{\underline{1}}{R'HC{=}CH{-}\Sigma} + R_3SnH \xrightarrow{60-80^\circ} \underset{\underline{2}}{R'\underset{\substack{|\\ SnR_3}}{HC}{-}CH_2{-}\Sigma} \qquad \begin{array}{l} R' = Me,H \\ R = Ph,Bu \\ \Sigma = CN, CH_2CN, COOMe,\ COOH, \\ \quad CH(OEt)_2, Ph \end{array} \tag{1}$$

$$\text{Initiator} \rightarrow 2I^\cdot \tag{2}$$

$$I^\cdot + R_3SnH \rightarrow R_3Sn^\cdot + IH \tag{3}$$

$$R_3Sn^\cdot + CH_2{=}CHR' \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_3Sn{-}CH_2{-}\dot{C}HR' \tag{4}$$

$$R_3Sn{-}CH_2{-}\dot{C}HR' + R_3SnH \xrightarrow{k_2} R_3Sn{-}CH_2{-}CH_2R' + R_3Sn^\cdot \tag{5}$$

In the case of styrene, however, very little isomerization occurs for cis- and trans-β-deuterated styrenes, indicating k_{-1} is smaller for styrenes than for hexenes (and presumably for any unsubstituted alkene).[19] This is due to the fact that the activation energy loss from the resonance stabilized benzyl radical is greater than that for the same reaction of simple sec-alkyl radicals.

The addition of organotin hydrides to fluoro- and perfluoro-olefins has been studied by Clark and co-workers.[21-24] A mixture of 1,1,2-trifluoroethene and $(CH_3)_3SnH$, when heated at 25° for 6 hr under irradiation, gave equimolar amounts of 1,1,2-trifluoro-1-trimethylstannylethane and 1,1,2-trifluoro-2-trimethylstannylethane in 93% total yield.[24] Perfluoropropene, treated analogously, gave equimolar amounts of both the 1- and 2-trimethylstannyl substituted isomers.[24] For difluoro substitution, 1,1-difluoroethene gave only the 2-trimethylstannyl adduct in quantitative yield, whereas, for monofluorosubstitution, vinyl fluoride gave no stable addition product with trimethyltin hydride.[24] Both free radical and ionic mechanisms were stated, but no attempt was made to determine which was operative.

ADDITION TO DIENES

Neumann and Sommer[25] treated various substituted 1,3-dienes with organotin hydrides and found that the stannyl group adds to the unsubstituted end of the diene and that 1,4-addition predominates. In later studies,[26] it was found that the type of addition, 1,2 or 1,4 depends strongly on the type of diene and tin hydride used, steric factors being relatively unimportant. Although 1,4-addition to dienes is dominant, both 1,3-cyclohexadiene and 1,3-pentadiene gave the 1,2-adduct as the major product when treated with Ph_3SnH Cyclopentadiene, however, gave over 90% 1,4-addition.[26]

The addition of Me_3SnH to 1,3-butadiene gave 38% trans-crotyltrimethyltin and 55% of the cis isomer.[27] This is exceptional since the trans product is usually favored in a free radical process. Two intermediates were proposed to explain this, one having the lone electron delocalized in a d orbital of tin and the second being a π-complex of trimethyltin radical and 1,3-butadiene.[27]

Neumann and co-workers[28] studied the stannyl radical addition to 1,3-

pentadiene and found that attack at the internal double bond is much more readily reversible than at the terminal position and leads to isomerization. The molar ratio of hydride to diene was found to be important for this process. By treating pure cis-1,3-pentadiene with Me_3SnH in a 1:2 molar ratio at 80° with AIBN, an equilibrium mixture of 4 products was obtained.[29] Analogous treatment of the trans isomer gave the same results.

Kuivila,[30] in a study of the addition of trimethyltin hydride to allene and four methyl-substituted allenes, found that, with the exception of allene itself, attack of the stannyl radical occurs predominately at the center carbon of the allene system.

ADDITION TO α,β-UNSATURATED KETONES

Early studies on addition of organotin hydrides to α,β-unsaturated ketones showed that selective reduction of the carbonyl group was the only reaction observed.[31-33] However, recent work by Pereyre and Valade[34] indicates that organotin hydrides may reduce the olefinic bond or may add 1,4 to the α,β-unsaturated system as illustrated with mesityl oxide, 3, in equation (6).

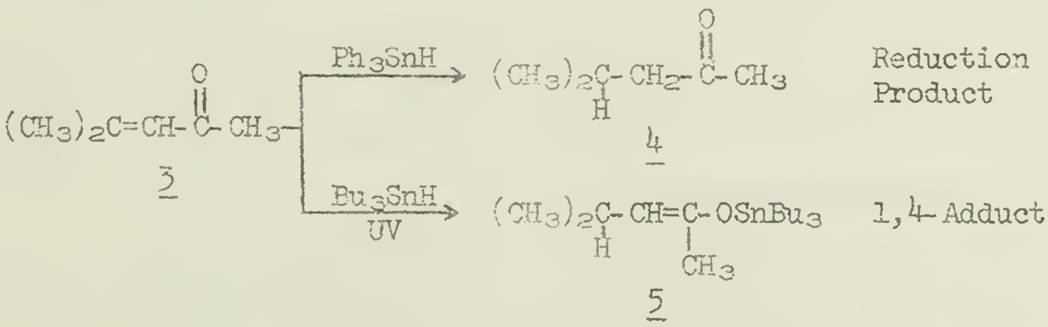
Leusink and Noltes[35] treated the ketones in Table I with various organotin hydrides in the absence of solvents and catalyst and found no significant formatio of α,β-unsaturated alcohols but rather mixtures of compounds 6-8 in equation (6b).

Table I shows that the primary step in the reaction of Bu_3SnH and Ph_3SnH with chalcone and phenyl vinyl ketone is formation of the 1,4-adduct, 6. The reaction stops at this stage for trialkyltin hydrides, but Ph_3SnH may react further with 6 under appropriate conditions to produce 7 by a hydrogenolysis reaction. The small amount of 7 produced when Bu_3SnH is used was ascribed to hydrolysis of 6.

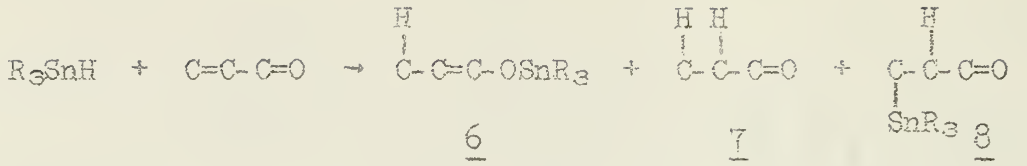
Creemers and Noltes[36] have investigated the hydrogenolysis reaction of triethyltin alkoxides, Et_3SnOR where R = Ph, t-Bu, and have shown that the reactions are strongly dependent on solvent polarity and are not markedly affected by radical initiators or scavengers. Thus, the hydrogenolysis reaction is believed to proceed by an electrophilic attack of the organotin hydride hydrogen on oxygen. Since Bu_3SnH is a poorer electrophile than Ph_3SnH, reactions of Bu_3SnH with chalcone and phenyl vinyl ketone stop at the 1,4-stage, while Ph_3SnH and ketone may go completely to the reduction product, 7, via a hydrostannation reaction followed by a hydrogenolysis.[35] In reactions using Ph_3SnH, where only 7 and 8 were formed, hydrogenolysis is so much faster than 1,4-addition that 6 is immediately consumed to form 7.[35]

It was found that 4-methyl-3-penten-2-one was reduced with Ph_3SnH to 4-methyl-2-pentanone upon heating at 150° for 5 hr and no addition product could be detected.[37] However, trialkyltin hydrides reacted in the expected manner, yielding primarily 1,4-addition with only small amounts of the reduction product 7.[37] Routes for the formation of both 6 and 7 were proposed in equations (7) and (8).

An ionic mechanism could also afford an explanation but is not likely under the reaction conditions.


$(CH_3)_2C{=}CH{-}C(=O){-}CH_3$
3
Ph_3SnH
$(CH_3)_2CH{-}CH_2{-}C(=O){-}CH_3$
4
Reduction Product
Bu_3SnH
UV
$(CH_3)_2CH{-}CH{=}C(CH_3){-}OSnBu_3$
5
1,4-Adduct

(6)



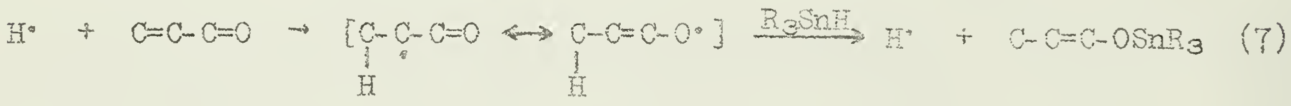
$$R_3SnH + C{=}C{-}C{=}O \rightarrow \underset{\underline{6}}{\overset{H}{C}{-}C{=}C{-}OSnR_3} + \underset{\underline{7}}{\overset{H}{C}{-}\overset{H}{C}{-}C{=}O} + \underset{\underline{8}}{\overset{H}{C}{-}\underset{SnR_3}{C}{-}C{=}O} \qquad (6b)$$

Table I

Ketone	Hydride	Ketone:Hydride Molar Ratio	Yield	Reaction Conditions	Molar Ratio 6	7	8
Chalcone	Bu_3SnH	1:1	90%	5 hr, 70°	90	10	-
"	"	1:1	80%	6 hr, 70°	100	-	-
"	Ph_3SnH	3:1	70%	3 hr, 55°	40	60	-
"	"	1:2	90%	"	40	60	-
"	"	1:3	75%	"	50	50	-
"	"	1:3	80%	5 hr, 55°	-	100	-
"	Ph_2SnH_2	1:1	55%	3 hr, 55°	-	100	-
Phenylvinyl-ketone	Bu_3SnH	1:1	60%	6 hr, 55°	95	5	-
	"	3:4	45%	20 hr, 55°	85	15	-
"	Ph_3SnH	3:4	60%	3 hr, 55°	70	30	-
"	"	1:2	85%	4 hr, 55°	-	100	-
"	Ph_2SnH_2	3:4	25%	2 hr, 55°	-	100	-
Methylvinyl-ketone	Bu_3SnH	1:1	0%	12 hr, 55°	-	-	-
"	Ph_3SnH	2:1	80%	3 hr, 55°	-	45	55
"	"	1:1	60%	4 hr, 55°	-	35	65
"	"	1:2	80%	3 hr, 55°	-	35	65
"	"	1:2	65%	2 hr, 55°	-	30	70

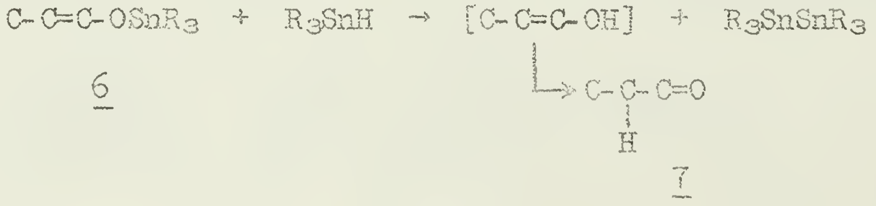
1,4-Adduct Formation

$$R_3SnH \xrightarrow{UV} R_3Sn^\bullet + H^\bullet$$



$$H^\bullet + C{=}C{-}C{=}O \rightarrow [\underset{H}{C}{-}\dot{C}{-}C{=}O \longleftrightarrow \underset{H}{C}{-}C{=}C{-}O^\bullet] \xrightarrow{R_3SnH} H^\bullet + C{-}C{=}C{-}OSnR_3 \qquad (7)$$

Reduction Product Formation



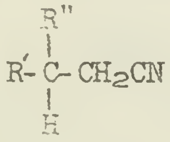
$$\underset{\underline{6}}{C{-}C{=}C{-}OSnR_3} + R_3SnH \rightarrow [C{-}C{=}C{-}OH] + R_3SnSnR_3 \qquad (8)$$

$$[C{-}C{=}C{-}OH] \rightarrow \underset{\underline{7}}{C{-}\underset{H}{C}{-}C{=}O}$$

ADDITIONS TO α,β-UNSATURATED NITRILES

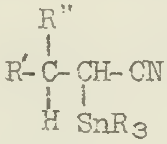
Contrary to first reports,[1] organotin hydrides were found to add to the double bond of acrylonitrile to form both the α- and β-stannyl adducts.[9] The α-adduct may form in the absence of AIBN and also, if AIBN is added to the reaction, the rate of formation of the β-adduct is considerably enhanced but that of the α-adduct is unaffected.[8] By increasing solvent polarity, a negligible solvent effect for the formation of the β-adduct occurred while an increase in the amount of the α-adduct was noted; hence, it was suggested that the α-adduct was formed by a polar mechanism and the β-adduct by a free radical process.[8] These facts suggest that the rate determining step in the polar reaction is nucleophilic attack of organotin hydride hydrogen on the β-carbon.

Pereyre and co-workers[38] treated the three α, β-unsaturated nitriles in Table II with organotin hydrides and found three products, 9, 10, and 11.


$\mathrm{R'{-}\overset{\displaystyle R''}{\underset{\displaystyle H}{C}}{-}CH_2CN}$

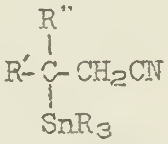
9

Reduction Product


$\mathrm{R'{-}\overset{\displaystyle R''}{\underset{\displaystyle H}{C}}{-}\underset{\displaystyle SnR_3}{CH}{-}CN}$

10

α-Adduct


$\mathrm{R'{-}\overset{\displaystyle R''}{\underset{\displaystyle SnR_3}{C}}{-}CH_2CN}$

11

β-Adduct

Table II

Hydride	Nitrile	% Red. 9	% Addition		Decomp. of Hydride to R_3SnSnR_3
			10	11	
Ph_3SnH	Ac[b]	0	0	98	
	Crot.[c]	30	0	0	+
Thermal[a]	DiMe Ac[d]	9	0	0	+
Bu_3SnH	Ac	7	55	36	
	Crot.	24	64	0	
Thermal	DiMe Ac	4	0	0	+
Bu_3SnH	Ac	0	0	56	
	Crot.	5	29	54	
UV	DiMe Ac	24	68	0	

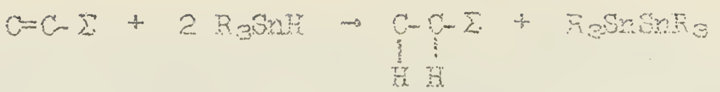
[a] Thermal conditions were 150° for 5 hr. [b] Acrylonitrile. [c] Crotononitrile. [d] Dimethylacrylonitrile.

Replacing the -CN group by the less electron withdrawing carboethoxyl group causes a decrease or total disappearance of the α-adduct, 10. For example, acrylonitrile treated with Bu_3SnH under thermal conditions yielded 55% α-adduct, 10, and 36% β-adduct, 11, whereas ethyl acrylate yielded no α-adduct and 83% β-adduct.[38] This supports an ionic mechanism for the formation of the α-adduct.

It is possible to reduce α, β-unsaturated nitriles and esters to the saturated compounds in low yield (equation 9) by either treatment at 150° for 5 hr or irradiation at 70° for 18 hr.[39]

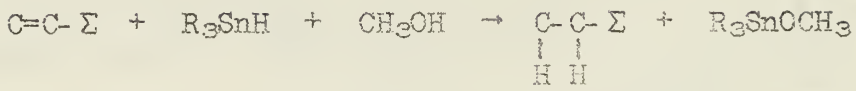
Reaction (9) proceeds by two steps: formation of the α-adduct followed by hydrostannolysis of the α-adduct.[39] The β-adduct will not undergo the latter step. Heating the α-adduct with methanol affords better yields of the saturated compound.[39]

The best method for reduction of α, β-unsaturated nitriles and esters is to heat equimolar amount of organotin hydride and either nitrile or ester with methanol as in equations(10), which again goes by the two step process.[39] Hence, specific deuterations of α, β-unsaturated nitriles and esters are possible. Pereyre and Valade[40] prepared compounds 12, 13, and 14.



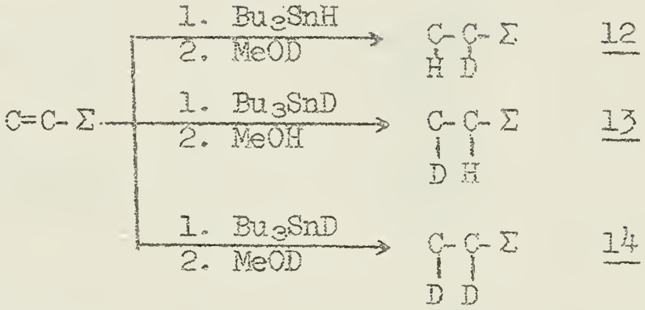
$$\mathrm{C{=}C{-}\Sigma \;+\; 2\,R_3SnH \;\rightarrow\; \underset{H}{C}{-}\underset{H}{C}{-}\Sigma \;+\; R_3SnSnR_3} \qquad (9)$$

Σ = CN, COOR'   R = Ph, Bu



$$\mathrm{C{=}C{-}\Sigma \;+\; R_3SnH \;+\; CH_3OH \;\rightarrow\; \underset{H}{C}{-}\underset{H}{C}{-}\Sigma \;+\; R_3SnOCH_3} \qquad (10)$$

Σ = CN, COOR'   R = Ph, Bu



Σ = CN, COOR

POLAR VS. FREE RADICAL MECHANISM

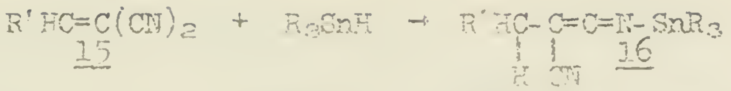
If the olefinic bond is strongly polarized as in alkylidenemalonitriles, 15, the organotin hydride may add by a polar mechanism to form N-stannylketeneimines, 16, as in equation (11).[41]

Replacing the cyano group in 15 by less polarizing COOR groups or substituting electron donors at R' was found to slow reaction (11) while electron withdrawing groups accelerated the reaction.[41] Alkylidenecyanoacetates, 17a, and alkylidenemalonic esters, 17b, also react with organotin hydrides by 1,4-addition (equation 12) to give ketene ethyl stannylacetals, 18, but sometimes so slowly that 1,2-hydrostannation of the olefinic linkage occurs. Also, certain vinyl ketones, 19, react exclusively by 1,4-addition giving enol ethers, 20, as shown in equation (13).[41] Steps (14) and (15) show the polar mechanism consistent with the formation of 1,4-addition products in (11), (12), and (13).[42]

The rate determining step is a nucleophilic attack of hydride hydrogen on the electron deficient β-carbon atom of 21 followed by fast attack of the stannyl cation.[42] Since the existence of free hydride ion is unlikely in the mixture, the primary step is most likely a hydride transfer.[42]

The polar mechanism has also been shown to be operative in the addition of triethyltin hydride to various isocyanates,[43] (16). Reaction (16) was found to be accelerated by polar solvents but could not be accelerated by radical initiators or be retarded by radical scavengers such as galvinoxyl. The probable mechanism is nucleophilic attack of the organotin hydride hydrogen on carbon,[44] (17), followed by rapid attack of the stannyl cation, (18).

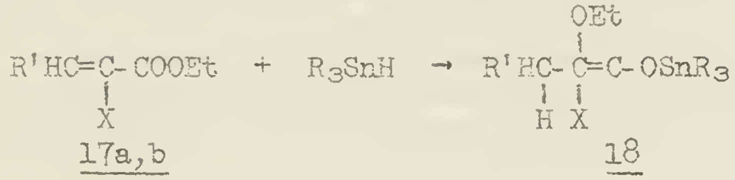
Polar mechanisms for organotin hydride attack can also be found for hydrostannation of carbonyl groups adjacent to strong electron withdrawing substituents. Treatment of chloral, 22, with organotin hydride yields both a 1:1 and 1:2 adduct, 23 and 24 respectively,[45] illustrated in equation (19). With stronger electron withdrawing substituents on the carbonyl group, such as in 2,2,2-trifluoroacetophenone, the 1:1 adduct is formed exclusively.[46] Equation (20) shows the proposed pathway for the 1:1 adduct.



$$\underset{\underline{15}}{R'HC{=}C(CN)_2} + R_3SnH \rightarrow \underset{\underline{16}}{R'\underset{H}{C}H{-}\underset{CN}{C}{=}C{=}N{-}SnR_3} \qquad (11)$$

R' = CH_3, EtO, Ph, p-$(CH_3)_2NC_6H_4$-, p-$CH_3OC_6H_4$-, p-ClC_6H_4-, p-$NO_2C_6H_4$-, and furyl

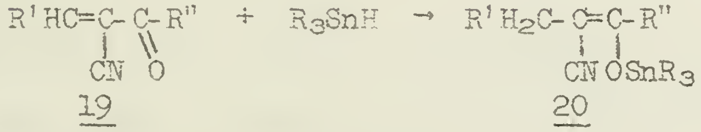
R = Et, Bu [also $R'_2C{=}C(CN)_2$ reacted as in (11)]



$$\underset{\underline{17a,b}}{R'HC{=}\underset{X}{C}{-}COOEt} + R_3SnH \rightarrow \underset{\underline{18}}{R'\underset{H}{H}C{-}\underset{X}{C}{=}\overset{OEt}{C}{-}OSnR_3} \qquad (12)$$

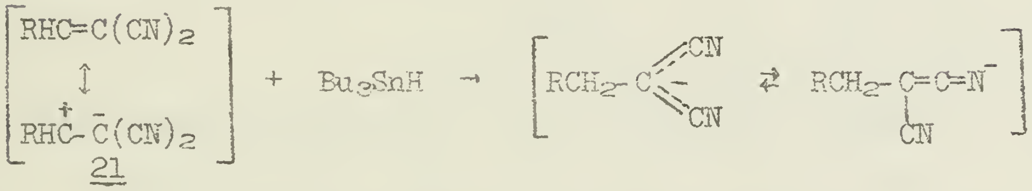
17a, X = CN: R' = Me, ∅, p-$CH_3C_6H_4$-, p-ClC_6H_4-

17b, X = COOEt; R' = Me, ∅

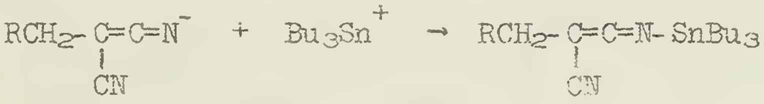


$$\underset{\underline{19}}{R'HC{=}\underset{CN}{C}{-}\underset{O}{\overset{\|}{C}}{-}R''} + R_3SnH \rightarrow \underset{\underline{20}}{R'H_2C{-}\underset{CN}{C}{=}\underset{OSnR_3}{C}{-}R''} \qquad (13)$$

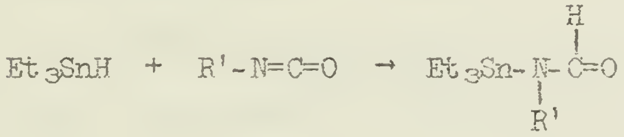
R' = p-$MeOC_6H_4$-, Ph, p-$NO_2C_6H_4$-, furyl; R" = Ph



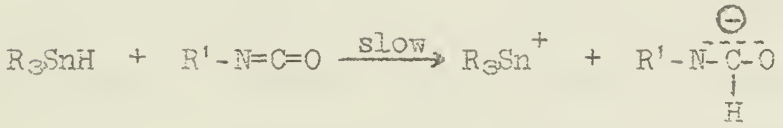
$$\underset{\underline{21}}{\left[\begin{array}{c} RHC{=}C(CN)_2 \\ \updownarrow \\ RH\overset{+}{C}{-}\overset{-}{C}(CN)_2 \end{array}\right]} + Bu_3SnH \rightarrow \left[RCH_2{-}C\begin{array}{l} \cdots CN \\ - \\ \cdots CN \end{array} \rightleftarrows RCH_2{-}\underset{CN}{C}{=}C{=}N^- \right] \qquad (14)$$



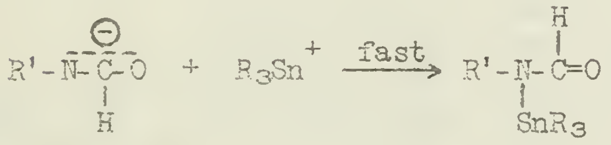
$$RCH_2{-}\underset{CN}{C}{=}C{=}N^- + Bu_3Sn^+ \rightarrow RCH_2{-}\underset{CN}{C}{=}C{=}N{-}SnBu_3 \qquad (15)$$



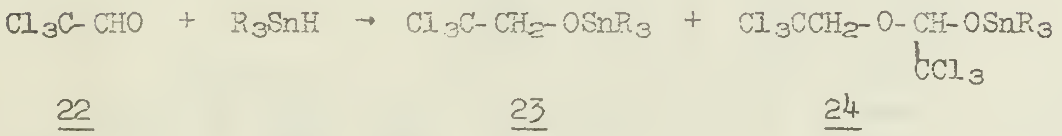
$$Et_3SnH + R'{-}N{=}C{=}O \rightarrow Et_3Sn{-}\underset{R'}{N}{-}\overset{H}{C}{=}O \qquad (16)$$



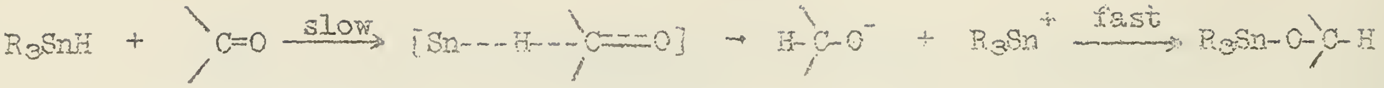
$$R_3SnH + R'{-}N{=}C{=}O \xrightarrow{slow} R_3Sn^+ + R'{-}\overset{\ominus}{N{\cdots}\underset{H}{C}{\cdots}O} \qquad (17)$$



$$R'{-}\overset{\ominus}{N{\cdots}\underset{H}{C}{\cdots}O} + R_3Sn^+ \xrightarrow{fast} R'{-}\underset{SnR_3}{N}{-}\overset{H}{C}{=}O \qquad (18)$$



$$\underset{\underline{22}}{Cl_3C{-}CHO} + R_3SnH \rightarrow \underset{\underline{23}}{Cl_3C{-}CH_2{-}OSnR_3} + \underset{\underline{24}}{Cl_3CCH_2{-}O{-}\underset{CCl_3}{C}H{-}OSnR_3} \qquad (19)$$



$$R_3SnH + >C{=}O \xrightarrow{slow} [Sn{-}{-}{-}H{-}{-}{-}C{=}{=}{=}O] \rightarrow H{-}C{-}O^- + R_3Sn^+ \xrightarrow{fast} R_3Sn{-}O{-}C{-}H \qquad (20)$$

CONCLUSION

Organotin hydrides are capable of adding to olefinic linkages to form either trialkyltin adducts or reduction products depending on the reaction conditions employed. Also, α,β-unsaturated ketones, nitriles, and esters may yield products derived from 1,4-addition to the conjugated system. Radical mechanisms for hydrostannation appear to occur in a majority of cases but polar mechanisms are known to be operative when the olefinic linkage has strongly polarizing substituents.

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ANGULAR SUBSTITUENTS VIA CYCLOPROPANE RING OPENING

Reported by Tadahiro Sasaki January 7, 1971

The nature of carbon-carbon cleavage in cyclopropane derivatives is a problem of mechanistic interest. The relatively high reactivity of this family of compounds also gives them potential preparative value in syntheses of fused cyclic systems possessing angular substituents. As knowledge of stereospecific formation and opening of cyclopropane rings accumulates, such practical applications of cyclopropane ring openings will increase. However, the results obtained in rather simple cyclopropane derivatives may have to be modified for fused cyclic systems by factors such as ring strain and steric accessibility to attacking reagents.

Acid catalyzed ring opening was used in several steroidal systems to introduce an angular methyl group (at 10β,[1] 10α,[2] and 5α[3] positions) and to obtain 19-labeled compounds.[4] An excellent application of acid catalyzed ring opening is the stereoselective and quantitative synthesis of 1-valeranone[5] from the methoxycyclopropane 1. The same methoxycyclopropane scheme was employed to synthesize 9,10-dimethyl-*trans*-decalones.[6] Further examples of acid catalyzed ring opening to generate angular substituents are: laurinterol 2 to give its isomeric ether, aplysin;[7] lumicholestenone (a photoisomer of 4-cholesten-3-one) to give 5α-chloro-10α-cholestan-2-one;[8] tricyclo[4.4.1.$0^{1,6}$]-undec-8-en-3-one to give tetrahydro-2-naphthalenone derivatives (two isomers);[9] 9,10-methylene-*cis*-2-decalone 3 (X = Y = H) to give 10-methyl-$\Delta^{1(9)}$-2-octalone.[10]

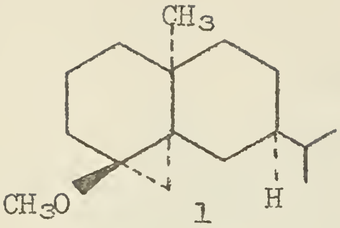
When electron withdrawing groups were present on the cyclopropane ring, the cyclopropyl ketones 3 underwent base catalyzed ring opening with ease to generate angular substituents.[11] In the case of X = Y = H in 3, self-condensation might take place,[9] but the corresponding system in the steroids gave an angular methyl group at the 10 position (α[3] and β[3,4,12] configurations). The cyclopropyl ester 4 gave a *cis*-fused perhydroindanyl keto acid upon saponification.[13]

An excellent general method for a stereospecific introduction of angular substituents is the reductive cleavage of α,β-cyclopropyl ketones with lithium in liquid ammonia.[13-16] Examples of such ketones are 4,5-methanosteroids,[15] a bicyclo[3.1.0]hex-3-en-2-one derivative,[16] and the keto acid 5.[13] The cyclopropane bond which is cleaved is the one possessing maximum overlap with the π-orbital of the carbonyl group.

The catalytic reduction of tricyclo[4.4.1.0]undecane gave 9-methyl decalins having a *cis-trans* ratio of 1,[17] and a similar result had been observed in a steroidal system.[3] Quite different from simpler bicyclobutane derivatives, hydrogenation of 6 afforded a dihydro derivative in good yield, generating an 8α-methyl group with concurrent formation of a double bond at C-6.[18] The presence of some special electronic and steric effects was suggested to account for the result.

The reactions of the bromocyclopropane 7 with nucleophiles were classified into three categorical types according to the nature of nucleophiles (ring opening to form 4a- or 10a-substituted compounds or substitution of bromine without ring opening).[19] A suggested mechanism involves the substituted cyclopropyl intermediate formed by displacement of bromine by a nucleophile.

Two other reaction types have been reported. The ring opening of the *trans*-cyclopropyl ketone 8 catalyzed by stannic chloride occurred with concerted double bond involvement to give only *trans* cyclized products (the *cis* isomer gave *cis* cyclized products).[20] Decarboxylative cyclopropane ring opening is another attractive method for angular methylation.[21,22]



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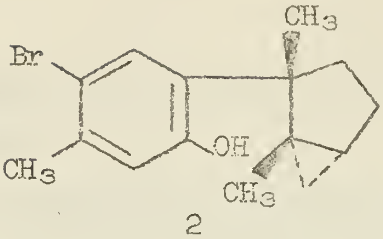

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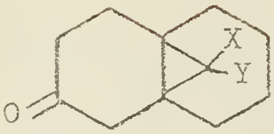

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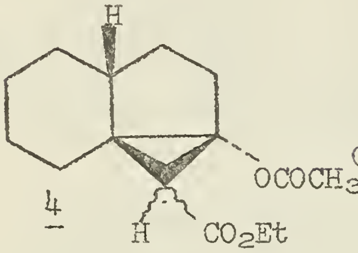

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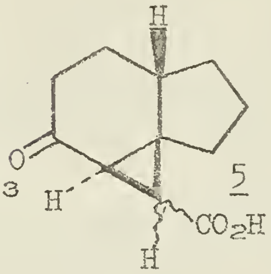

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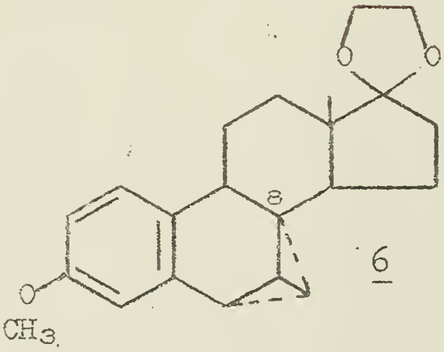

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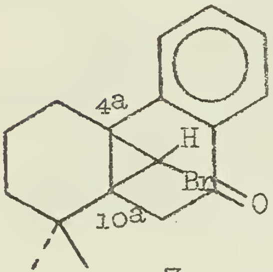

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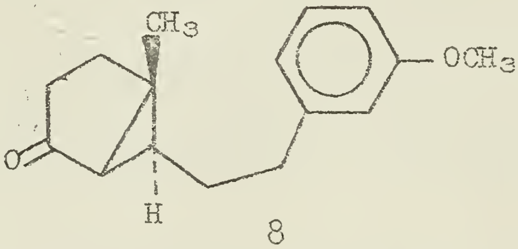

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THE PHOTOCHEMISTRY OF CONJUGATED CYCLOPROPYL KETONES

Reported by Willie B. Lunsford January 11, 1971

Saturated bicyclo [n.1.0] ketones in which the cyclopropyl ring is in conjugation with the carbonyl usually photoisomerize to cyclic enones when the rings are unsubstituted and when the photolysis is carried out in poor hydrogen-donating solvents. This is particularly true when the molecule contains the saturated bicyclo [3.1.0] or [4.1.0] system. For example, the vapor phase irradiation of bicyclo[3.1.0]hexan-2-one (1) affords 3-methyl-2-cyclopentenone (2) as the major product.[1-3] Presumably, the n → π* excitation leads to the rupture of the C_1-C_6 bond. The resulting intermediate 1a undergoes a 1,2-hydrogen migration to give the α,β-unsaturated ketone. A careful study of the path of the rearrangement indicates that two bonds, the C_1-C_6 and the C_1-C_5, are susceptible to cleavage. However, external C_1-C_6 bond rupture predominates. This has been attributed to π-assisted cyclopropyl bond fission, that is, to preferential cleavage of the cyclopropyl bond which best overlaps the π-system of the carbonyl. That this is the C_1-C_6, not the C_1-C_5, can be ascertained by inspection of Figure 1. The highly selective C_1-C_6 bond cleavage with subsequent α,β-unsaturated ketone formation has been observed in condensed phase photolyses of bicyclo [3.1.0] systems as well.[4,5]

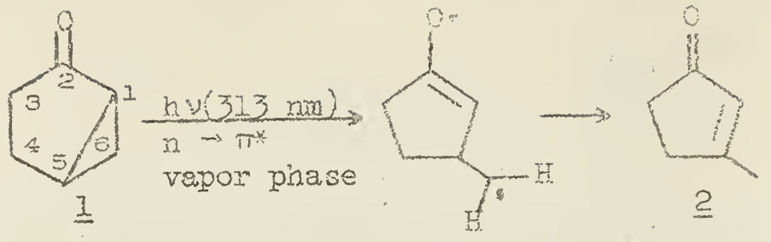
The importance of cyclopropyl bond-π carbonyl system overlap may also be assessed from the photolysis of various 3,5α-cyclocholestanes[6] and -androstanes.[7,8] A prime example is 3,5α-cycloandrostan-6-one (3) which upon irradiation affords enones 4, 5, and 6, all derived from internal C_3-C_5 bond rupture followed by hydrogen migration to C_3 or C_5.[8] Molecular models clearly show that the π-carbonyl system overlaps better with the internal C_3-C_5 bond in this case.[9]

Substituents alter the photochemistry of the bicyclo [3.1.0] system. For example, the photolysis of cis-5,6-diphenylbicyclo[3.1.0]hexan-2-one (7) results in the trans isomers 8a and 8b and the enone 9 which apparently comes from C_1-C_5 bond rupture followed by hydrogen migration to C_5.[10-12] The trans isomer 8a, derived from external C_1-C_6 bond cleavage and reclosure, makes up 85% of the total trans material while its enantiomer 8b, derived from internal C_1-C_5 bond cleavage and reclosure, makes up only 15%. Note that external C_1-C_6 bond fission still predominates and that phenyl migration (comparable to hydrogen migration in 1) does not occur. The photolysis of the trans isomer 8a affords a similar set of products. Trans to cis isomerization, however, reportedly proceeds with 100% external C_1-C_6 bond cleavage.

Bicyclo [4.1.0] systems undergo preferential external bond cleavage also.[13-17] However, an investigation of alkyl substituent effects reveals that the path of the photoisomerization can be altered.[13,14] For example, the irradiation of bicyclo[4.1.0]heptan-2-one (10a) follows exclusively path A affording enone 11a while its 3-methyl derivative 10b follows exclusively the two photon path B affording ultimately 13b. Methyl substituents can be arranged so that both or neither of these paths is followed.

Cis-bicyclo[6.1.0]nonan-2-one photoisomerize via a path similar to path B even without the 3-alkyl substituent.[18] In addition, trans-bicyclo[6.1.0]-nonan-2-one is formed.

Solvent affects the path of the photolysis of these systems. All of the above irradiations were carried out in aprotic or poor hydrogen-donating solvents When the irradiations are carried out in good hydrogen-donating solvents photoreductions to saturated ketones[16-19] or alcohols[16,17] are observed.



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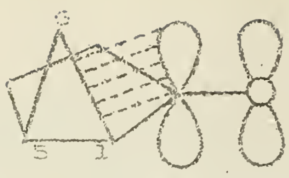
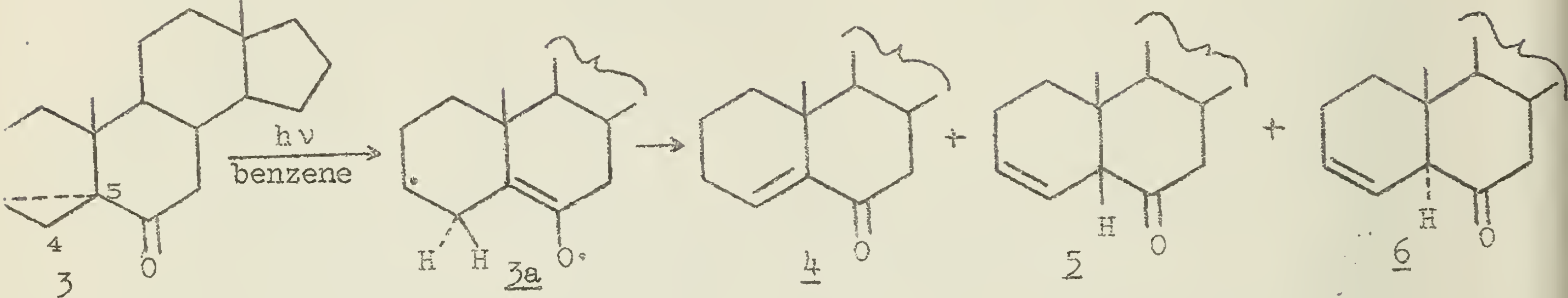
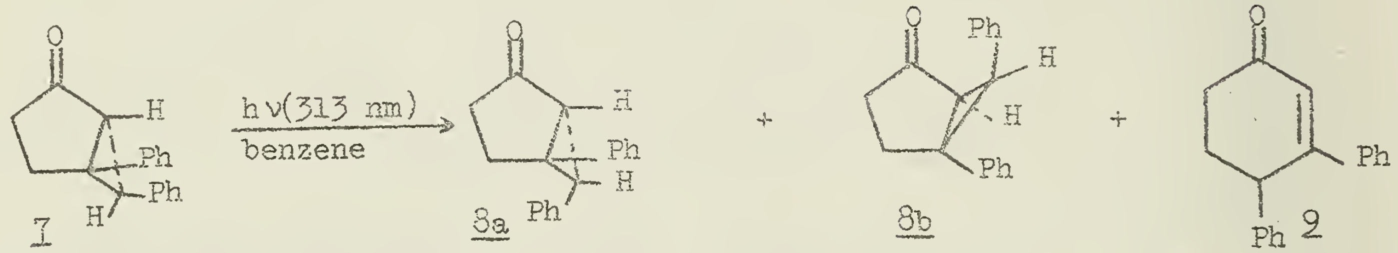


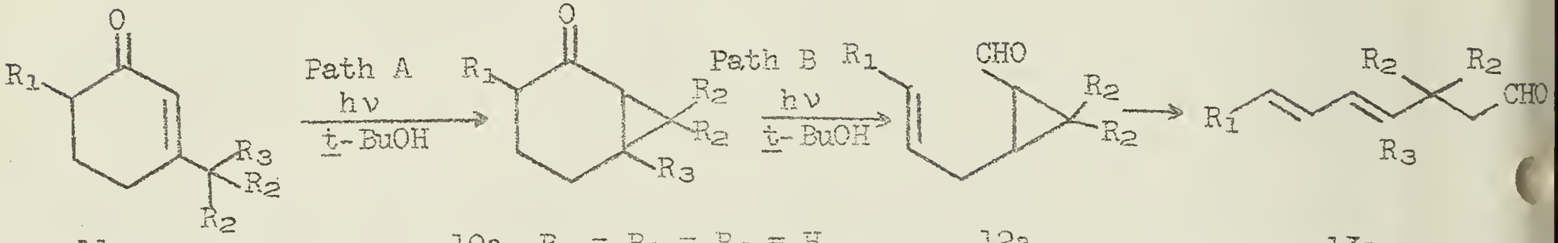
Figure 1



3 3a 4 5 6



7 8a 8b 9



11a
11b

10a, $R_1 = R_2 = R_3 = H$
10b, $R_1 = R_2 = H$; $R_3 = CH_3$

12a
12b

13a
13b

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ION CYCLOTRON RESONANCE SPECTROSCOPY IN ORGANIC CHEMISTRY

Reported by Jon T. O'Connor January 14, 1971

The theory and the instrumentation of ion cyclotron resonance spectroscopy have been adequately described.[1] Briefly, an ion cyclotron resonance spectrometer is a mass spectrometer, whose detection system is based on the following phenomenon. An ion of mass m and charge q, when placed in a uniform magnetic field H, will absorb energy from an alternating electric field whose frequency, w, equals w_c, the ion cyclotron resonance frequency of the ion. Equation 1 defines w_c. In absorbing this energy the velocity of the ion increases. This absorption is monitored and recorded in a linear scale in mass. Used simply as a mass spectrometer it holds no particular advantage over other methods. However, when there is a large concentration of neutral particles in addition to ions such that ion-molecular collisions and reactions can occur, the value of this technique becomes apparent. By increasing the velocity of one type of ion by means of a strong radiofrequency electric field at its ion cyclotron resonance frequency, there will be substantial changes occurring in the concentrations and velocities of other ions to which the first type is chemically coupled. The consequent changes in line shape and intensity can be observed with a weak radiofrequency field which can be scanning other masses.[1] This technique is similar to the double resonance technique in pmr spectroscopy.

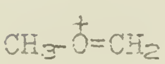
$$w_c = \frac{qH}{mc} \qquad (1)$$

Utilization of ion cyclotron resonance spectroscopy has been rather limited to date in the field of organic chemistry. Brauman and co-workers[2] have employed it in determining the relative gas phase acidities of a series of alcohols. They observed systems characterized by equation 2 and determined in which direction they proceeded by noting whether "heating" R_2O^- affected the signal of R_1O^- and, conversely, whether "heating" R_1O^- affected the signal of R_2O^-. They similarly determined the relative gas phase acidities of a series of amines[3] and a series of carbon acids.[4] Jaffé and co-workers[5] have determined the relative gas phase basicities of a series of dialkyl-N-nitrosamines. They also found evidence that suggests a McLafferty type rearrangement for the molecular ions of these compounds.[5a]

$$R_1OH + R_2O^- \rightleftarrows R_1O^- + R_2OH \qquad (2)$$

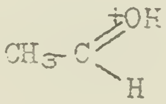
Djerassi and co-workers[6] have turned to ion cyclotron resonance spectroscopy in their attempt to determine the structure of the $C_3H_6O^{+}\cdot$ ion generated in the double McLafferty rearrangement of dialkyl ketones, which have a γ-hydrogen available for migration on both alkyl groups. Their results interestingly conflicted with the results of researches utilizing more usual methods of analysis.

Beauchamp and Dunbar[7] have suggested that, since ion-molecular reactions occurring at low pressure are sensitive to the nature of functional groups and the details of the molecular structure of both the ionic and neutral reactants, perhaps ion cyclotron resonance spectroscopy can be used to ascertain the specific reactivities of functional groups, which in turn can be used to characterize unknown ion structural features. They have looked at the reaction of three isomers of $C_2H_5O^+$ (1-3) and found they could distinguish between 1 and 2, 1 and 3, but not 2 and 3.

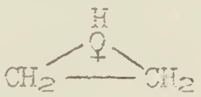


$CH_3-\overset{+}{O}=CH_2$

1



2



3

The remainder of the use of ion cyclotron resonance spectroscopy has consisted in observing the ion molecular reactions of various one- and two-component systems--acetonitrile, p-chloroethylbenzene,[9] methanol,[10] chloroethylene,[11] ethylene,[12,13] fluoroethylene,[13] acetylene,[14] methane,[15] perfluoroethane,[16] methane-nitrogen,[17] methane-hydrogen,[18] H_2S-ethylene,[19] H_2S-acetylene,[19] water-chloromethane,[20] water-chloroethane,[20] HCl-fluoromethane,[20] chloromethane-benzene,[21] acetonitrile-benzene,[21] and NO_2-benzene.[21]

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